Redox Aminations of Isatins

by

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Redox Aminations of Isatins

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Chairperson; Dr. Jon Tunge

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Abstract

This thesis details the development of a method for the synthesis of oxindoles containing an N1-C3 indole linkage while simultaneously oxidizing an indoline to an indole. This bond is made via redox amination, meaning no external oxidants or reductants are needed. This methodology was found to be compatible with a wide range of isatins, and was chosen as a strategy for synthesizing a library of oxindoles containing an N1-C3 linkage to either a pyrrole or an indole.

Next is detailed attempts to extend the tert-amino effect to synthesize pyrroles, along with unexpected results and preliminary findings. Finally, we report preliminary results on a palladium catalyzed decarboxylative amino allylation of isatins. In this methodology, an allyl amino ester is condensed with isatin. Upon treatment with palladium, decarboxylative allylation occurs to give a 3,3 disubstituted oxindole containing an allyl group and a free amine. The only stoichiometric byproducts of this reaction are CO_2 and acetone.

Acknowledgements

This project was done under of the supervision of Dr. Jon Tunge. I am forever indebted to him for his guidance and encouragement. Without him, I would not have been able to accomplish what I have.

I would like to thank Dr. Prashi Jain, who I worked with to make the library of oxindoles.

I would also like to give special thanks to Dr. Antonio Recio and Dr. Jimmie Weaver, who helped transform me from a kid with no lab skills to a competent chemist. I also want to thank Dr. Scott Petrich who first introduced me to organic chemistry and taught me that we are just carbon based molecules studying carbon based molecules.

I also must thank my family. They have been supportive and encouraging throughout my academic career. Specifically my wife Mary Peach-Partridge. You have been a source of encouragement and motivation throughout a difficult time. I do not know what the future holds, but I know I want you by my side for all of it.

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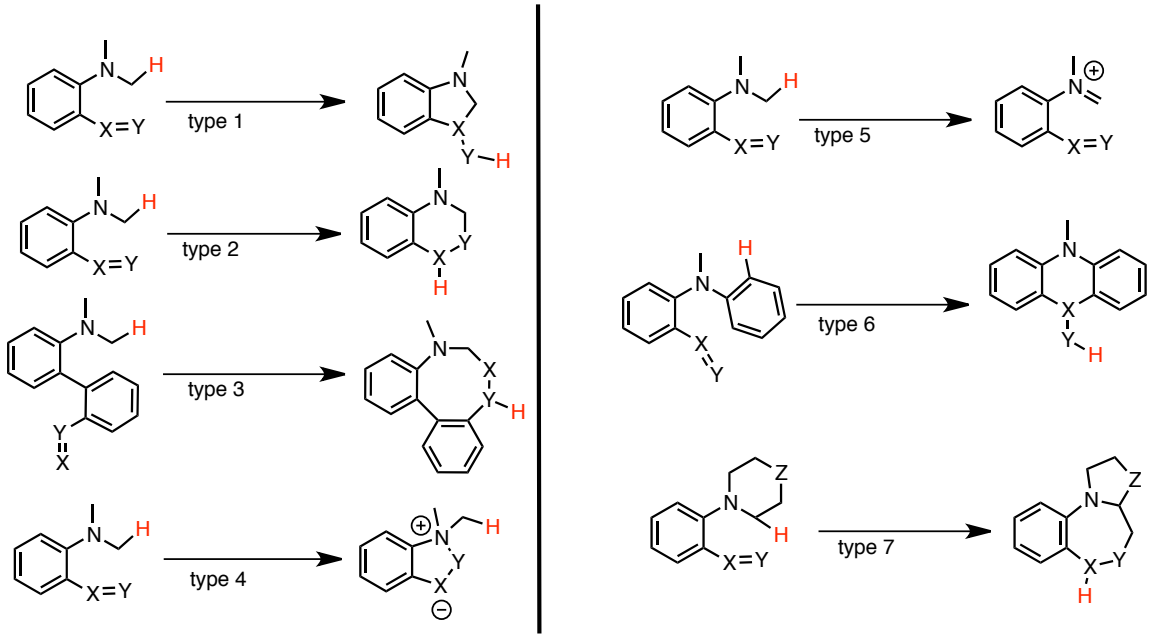
Chapter 1-1 Introduction to the tert-amino effect

Nine Nobel prizes in chemistry have been awarded to scientists who discovered new methods of generating new carbon-carbon bonds or carbon-heteroatom bonds.[1] This fact underscores the importance of finding and discovering new ways to make such bonds. With such a high reward for methods that can produce new carbon bonds, one would expect most organic chemists to have utilized and researched any and all ways of synthesizing new carbon bonds; yet this is not the case. No trend proves this more than the boom in methods to functionalize C–H bonds. The ability to take a carbon-hydrogen bond and transform it into a carbon-carbon or carbon-heteroatom bond is a quintessential goal of organic chemistry, as it would allow construction of complex molecules from simple precursors. While methods capable of C-H activation are well researched,[2] one particular type of C–H bond activation exists in relative obscurity in organic chemistry, namely the tert-amino effect.

The tert-amino effect refers to the reactivity observed when a tertiary aniline is allowed to react with an ortho substituent.[3] The tert-amino effect was discovered by Pinnow, and reported first in 1894.[4] For many years, various groups reported similar reactions involving a tertiary aniline reacting with a substituent in the ortho position.[5] One of those groups was that of Otto Meth-Cohn, who researched the subject from the 60's onward. It was Meth-Cohn who first coined the term "Tert-Amino Effect" in 1972. This was the first time that many of these reactions were grouped together under this term. In 1996, Meth-Cohn wrote a review, which divided the tert-amino effect reactions into five types based on the mechanism of reactivity and the size of the ring formed. In 2003, Quintela added to this catalog, describing type 6 and type 7 reactions (Table 1-1.1).

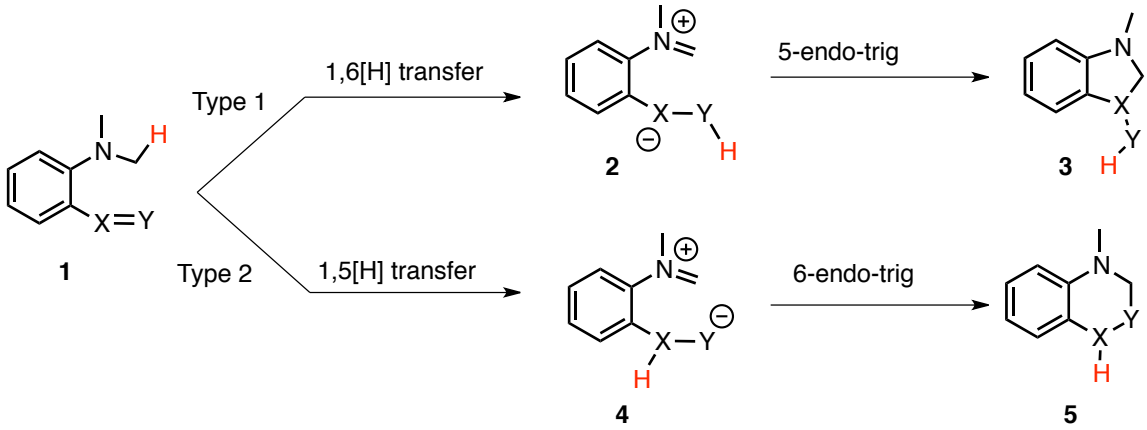
These classifications are not based on historical chronology, so the oldest known tert-amino effect reactions are classified as type 4. Tert-amino effect reactions encompass a broad class of carbon-carbon and carbon-heteroatom forming reactions and have found significant growth in recent years. Herein is a brief review of the tert-amino effect, with emphasis on type1 and type 2 tert-amino effect reactions.

Table 1-1.1: Types 1-7 Tert-Amino Effect Reactions



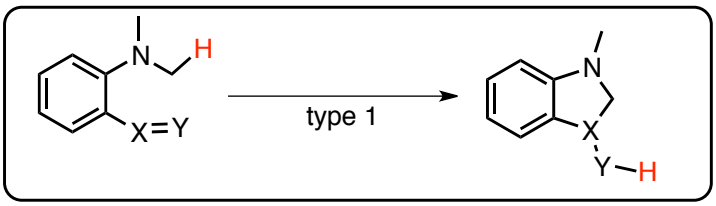
Chapter 1-2 The type 1 and type 2 tert-amino effect reactions

Figure 1-2.1: Type 1 and Type 2 mechanisms



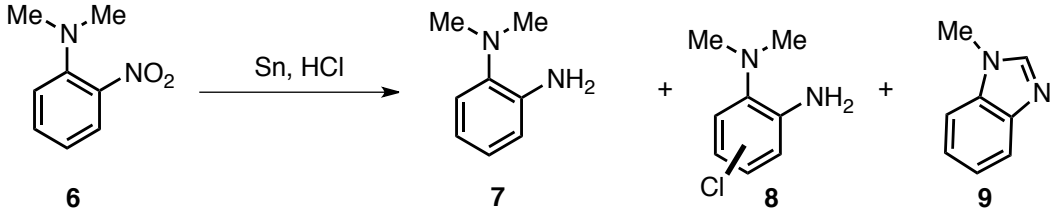
While unique enough to merit separate categorization, the type 1 and type 2 tert-amino effect reactions share many of the same traits. They both involve a tertiary aniline with an ortho substituent that contains a π bond (**1**, Scheme 1-2.1). In the type 1, the reaction begins with a 1,6-hydride transfer from the carbon adjacent to the tertiary amine to the ß atom (Y), forming an iminium ion and a benzyl anion **2**. The next step consists of a 5-endo-trig type cyclization to give a 5 member ring **3**. The type 2 tert-amino effect reaction follows the same trend of hydride transfer followed by cyclization, however it is initiated by a hydride transfer to the α atom (X), forming an anion at the ß atom **4**. This dipolar intermediate then undergoes a 6-endo-trig cyclization to furnish a six membered ring **5**. While type 1 and type 2 reactions occur through similar mechanisms, there is rarely any competition between the two mechanisms.[6] The main determinants of which path these reactions will take are the atoms that make up X=Y and the substituents attached to them. These determinants, as well as the history and mechanisms of the tert-amino effect will be explored in the following sections.

Chapter 1-3 The type 1 tert-amino effect reaction



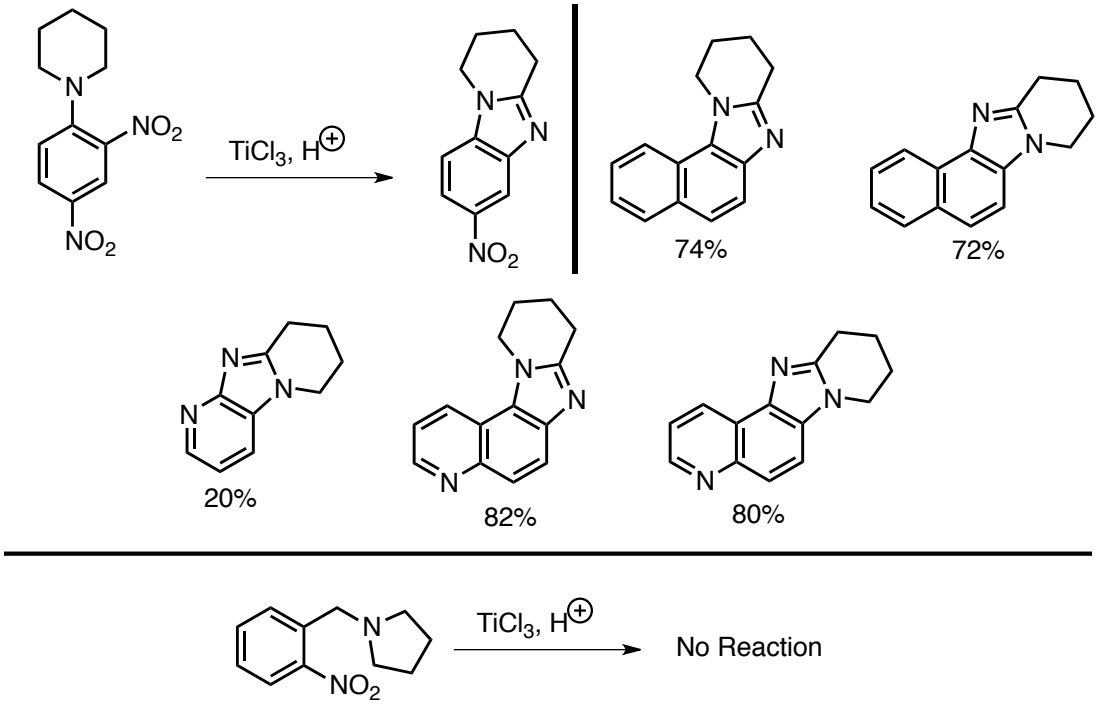
The type 1 tert-amino effect was discovered by accident and first reported in 1899 by Pinnow and coworkers.[7] While trying to reduce 2-nitro dimethylaniline (**6**, Scheme 1-3.1) using tin under acidic conditions, they observed the desired primary amine as well as chlorinated versions of that same amine, **7** and **8**, respectively. They also observed a

Scheme 1-3.1: First Known Type 1 Reaction



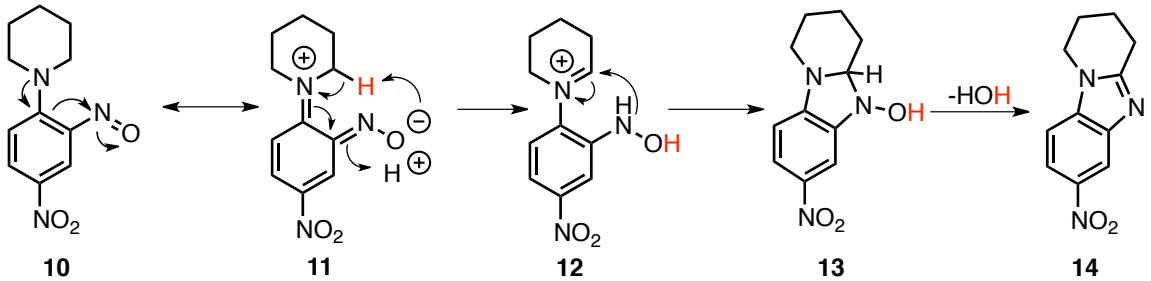
benzimidazole **9**. The formation of this benzimidazole became known as a functional group test for ortho nitration. Pinnow believed that the benzimidazole was formed by reaction with an intermediate nitroso group. While this method did yield benzimidazoles, it was not an effective method since yields were low and typically resulted in the formation of aniline. Benzimidazole yields were improved upon in 1968 by Suschitzky who used $TiCl_3$ to selectively reduce the ortho nitro to a nitroso group, which then reacted with the carbon adjacent to the tertiary amine (Table 1-3).[8] The ortho nitroso was shown to react with naphthalenes and quinolines in good yields. One thing that was necessary was for the tertiary amine to be an aniline, as a tertiary benzyl amine did not give any product.

Table 1-3.1: Benzimidizoles Via Type 1 Tert-Amino Effect.



The non-reactivity of the benzyl variant indicated that the amine had to be in a conjugated π system, presumably resonance activation in the form of **11** is required. This led the authors to suggest a mechanism (Scheme 1-3.2) where the oxygen of the nitroso group deprotonates the carbon adjacent to the tertiary iminium **11**. The hydroxylamine **12** then attacks the iminium to form dehydrobenzimidazole **13**, which aromatizes upon loss of water to yield product **14**.

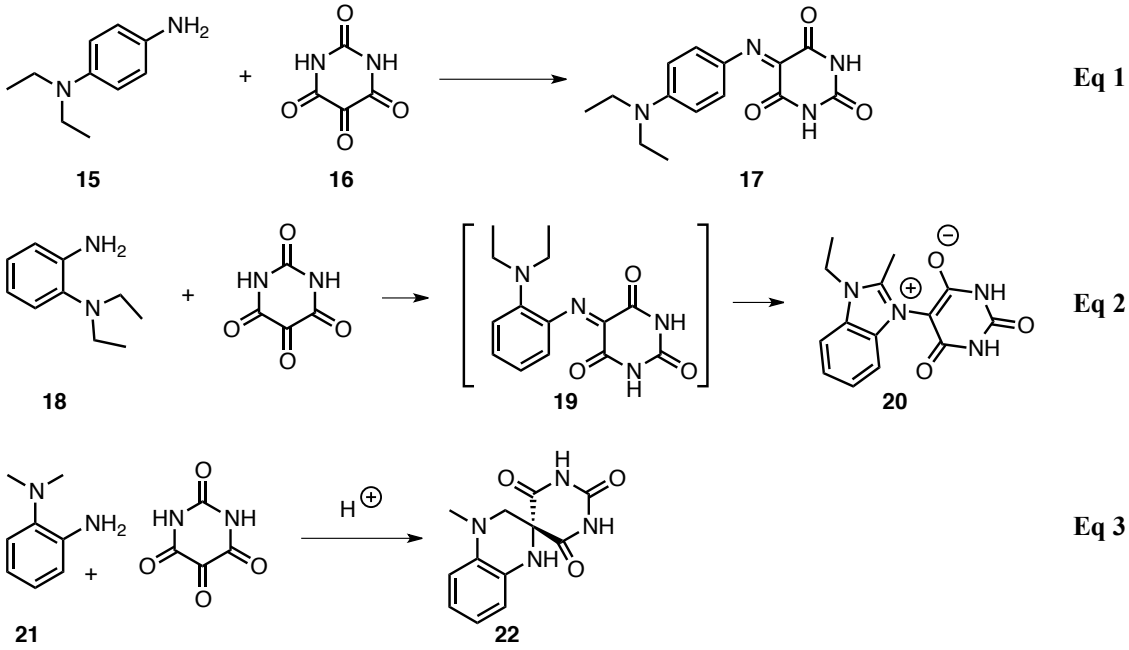
Scheme 1-3.2: Mechanism for Formation of Benzimidazoles



The reaction of tertiary anilines with ortho nitroso compounds appears to occur spontaneously under the conditions required to generate the nitroso compound, both by reduction of a nitro group or oxidation of an amine, and there are no reports of the isolation of a tertiary amine bearing an ortho nitroso compound. This reaction results in spontaneous formation of a C–N bond, which can be produced in high yields. The drawback is that with nitroso compounds there is no way to prevent the aromatization, and the reaction is limited to producing simple benzimidazoles. Nonetheless, the transformation is of interest since nitroso groups are typically not functionalities that are capable of undergoing such carbon-nitrogen bond forming reactions.

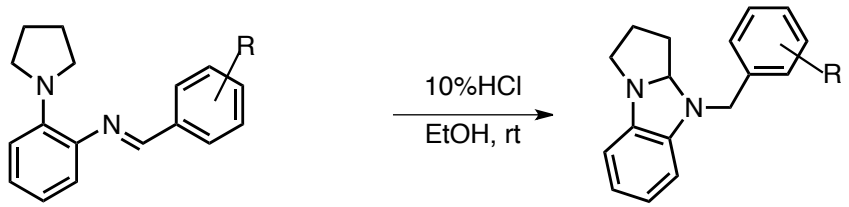
In 1938,[9] Cramer and coworkers were synthesizing dyes by combining alloxan and various anilines (Figure 1-3.1). While para substituted anilines such as *p*-diethyl amino aniline **(15)** condensed with alloxan **(16)** to give the predicted imines (Eq 1), anilines containing ortho tertiary amines gave products that were not predicted (Eq 2-3). While Cramer correctly predicted that this was due to the ortho substituent on the aniline, it was not until technology improved that the correct structure of these products was discovered.[10] The diethyl aniline **18** produced the 5-membered benzimidazolium zwitterion **20,** presumably through initial condensation to produce the imine intermediate **19**. Further oxidation to **20** is caused by exposure to air.

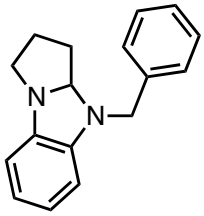
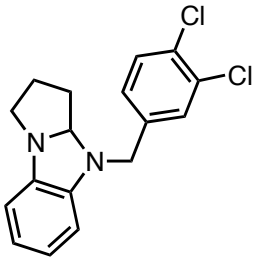
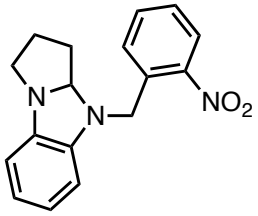
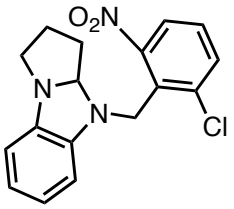
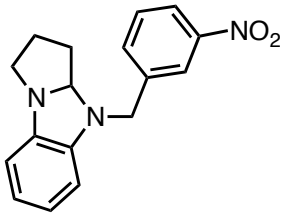
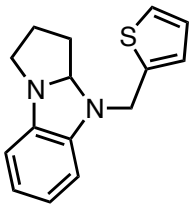
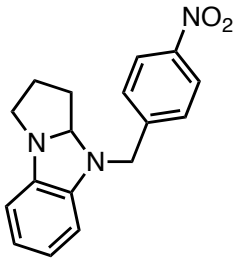
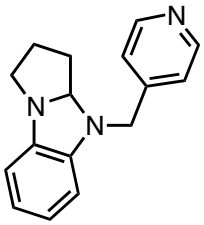
Figure 1-3.1: Type 1 Tert-Amino Effects With Imines



The dimethyl aniline **21** produced a spirocycle **22** (see type 2 tert-amino effect reactions, next section). It was inferred than these ortho anilines initially condensed with the ketone of alloxan and then underwent a carbon-nitrogen bond formation. In 1969, Otto Meth-Cohn explored this further. To determine if this reactivity was unique to imines derived from alloxan, he used imines derived from benzaldehydes (Table 1-3.2). The imines were formed from the corresponding benzaldehydes and aniline bearing a pyrrolidine at the ortho position by condensation in the presence of a drying reagent.

Table 1-3.2: Type 1 Tert-Amino Effect Reactions with Imines

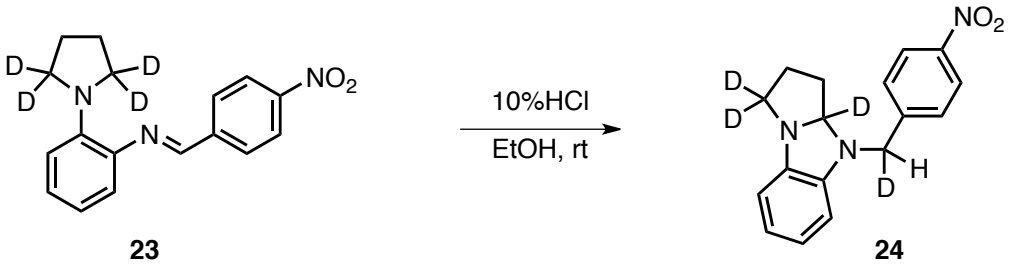


Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		89	5		84
2		86	6		96
3		82	7		85
4		85	8		87

The reaction produced a range of dihydrobenzimidazoles. Initially, benzaldehyde (Entry 1) was shown to produce the dihydrobenzimidazole in good yield. This reactivity was also observed with all of the isomers of nitrobenzaldehyde (Entries 2-4). Entry 2 is of particular interest, due to the ortho substitution on the benzaldehyde. In fact, the reaction

was successful with benzaldehydes containing ortho,ortho disubstitution (Entry 6). It was also found to be compatible with heteroaromatic aldehydes (Entries 7 and 8). Aldehydes with electron donating groups were also successful, but were found to precipitate out as the HCl salts.

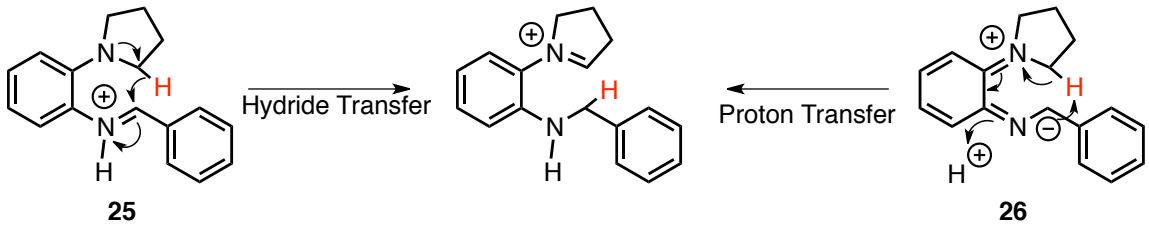
Scheme 1-3.3: Deuterium Labeling Study of Imines.



23 **24**

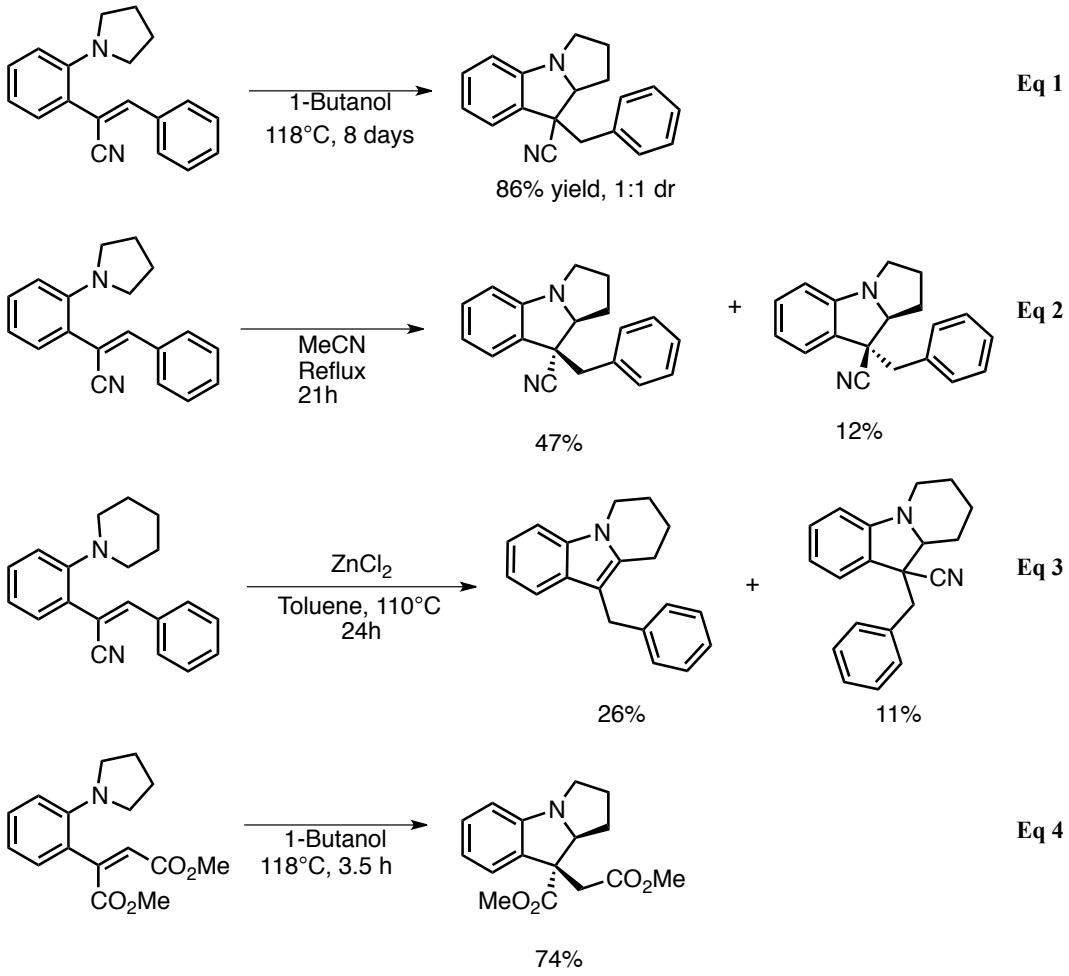
Through deuterium labeling (Scheme 1-3.3), it was found that a deuterated imine **23** will retain the deuterium in the product. This indicated that the proton in the product was derived intramolecularly, and not from the solvent or catalyst. Preliminary rate studies indicated that the deuterated molecule reacted 5.9 times more slowly that the protio analog, indicating that, the in the rate-determining step, a C–H bond is broken. It was not known if this hydrogen is transferred as a proton **26**, (Scheme 1-3.4) or as a hydride **25**. While this is a unique methodology in and of itself, it also demonstrates that by placing a different acceptor group (in this case a phenyl imine) ortho to a tertiary aniline, intramolecular reaction can occur. In 1972, Meth-Cohn grouped these and many other such reactions under the term "the tert-amino effect".[3] This review brought together many different types of reactions, and was instrumental in the boom in research in the tert-amino effect reactions that took place in the 1980's.

Scheme 1-3.4: Possible Rate Determining Steps



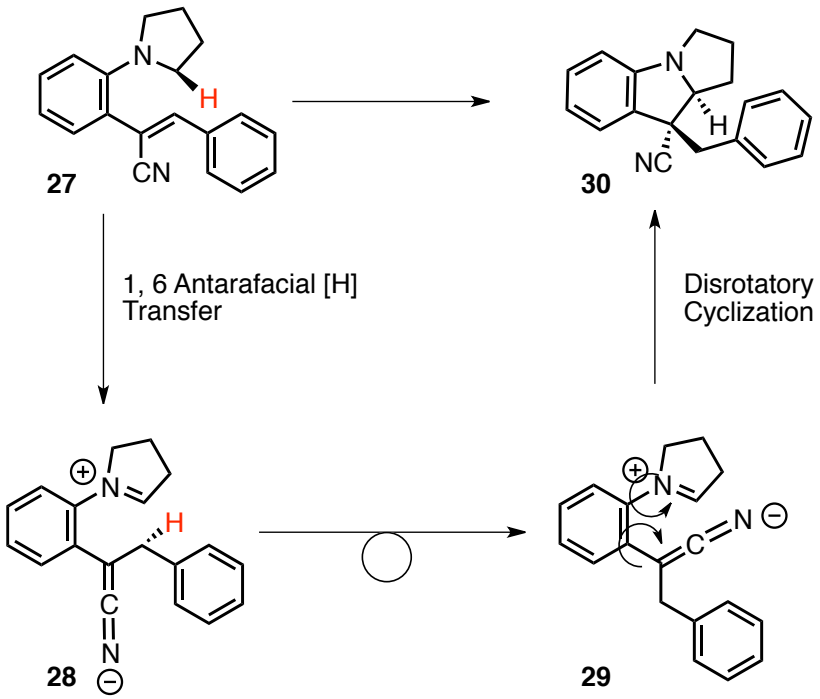
In 1984 Verboom and Reinhoudt showed that the tert-amino effect could be used to form new carbon-carbon bonds.[11] They did so by using styrenes containing an electron-withdrawing group on the α carbon (Scheme 1-3.5).

Scheme 1-3.5: Type 1 Tert Amino Raction Forming Carbon-Carbon Bonds



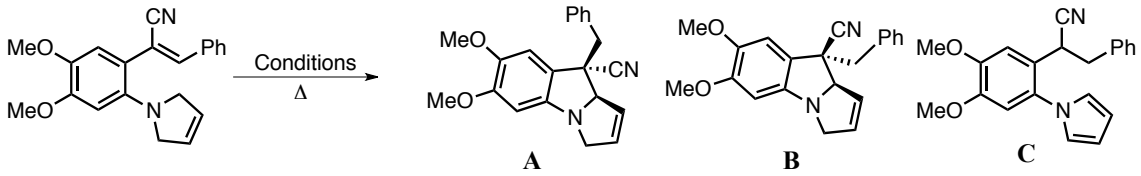
It was found that when reactions were carried out in butanol, high yields were observed but only after long reaction periods (Eq 1). With this new reaction came an issue that had not been dealt with before in such reactions, and that is the formation of diastereomers. Reaction in butanol produced a 50:50 mixture of diastereomers. Changing solvents to acetonitrile (Eq 2) improved the dr in a much faster time. When the reactant was changed from a pyrrolidine to a piperidine (Eq 3), the reaction required a $ZnCl_2$ catalyst and produced an indole as the main product. The highest diastereoselectivity was observed when the cyano group was replaced with an ester (Eq 4). This produced only one diastereomer and in good yield. Since this reaction is thermal and requires no catalyst, it is not likely that there is a proton transferred. This led the authors to propose a mechanism, which starts with a 1,6 antarafacial hydride transfer **28** (Figure 1-3.2).

Figure 1-3.2: Mechanism of Type 1 Tert-Amino Reaction



The resulting intermediate then cyclizes in a disrotory manner to yield the product in high diastereoselectivity. However, the low observed dr's resulted because the cyclization (**29 ➔30**) was found to be reversible, while the hydride transfer was not. Thus, epimerization could occur once the reaction finishes. The presence of an iminium in the reaction mechanism was proven accidentally by Reinhoudt and coworkers when attempting to synthesize analogs of mitomycin C.[12] They planned to use a tert-amino effect reaction (it was not yet called a type 1) to form an indoline fused to a pyrroline (Table 1-3.3). When they attempted the reaction in acetonitrile (Entry 1), they observed the two diastereomers of the desired product. Changing solvent to methanol (Entry 2) resulted in an unexpected side reaction as the main product. In it, the iminium isomerizes to a pyrrole instead of undergoing carbon bond formation.

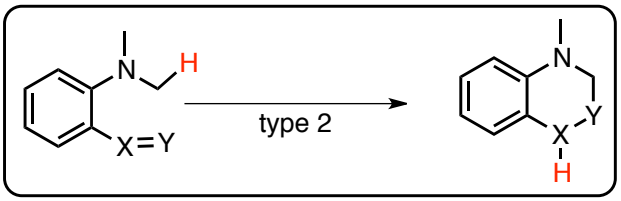
Table 1-3.3: Pyrroles via the Type 1 Tert-Amino Effect



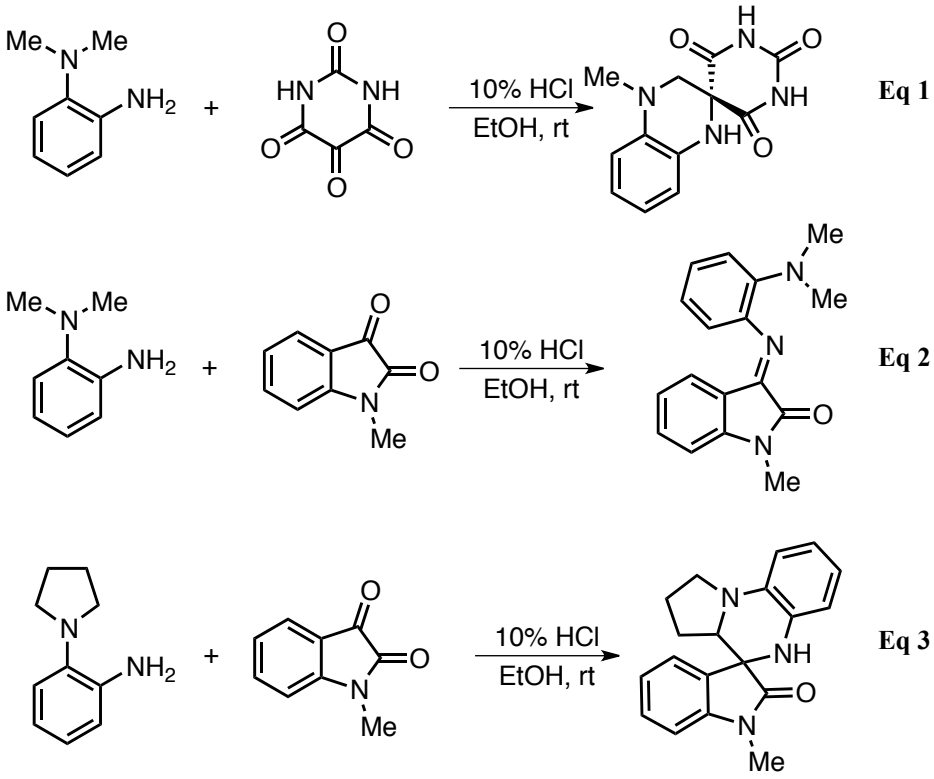
Entry	Solvent	Additive	Yield	Ratio A:B:C
1	MeCN	$ZnCl_2$	53%	1.8:1:0
2	Methanol	None	67%	1.4:1:5

The most likely explanation for this reactivity is that upon formation of the iminium, there is a deprotonation of the pyrrolinium to produce the aromatic pyrrole. It would seem that the pro-aromatic pyrroline favors aromatization over cyclization. Since it was not what the group was hoping for was reported but not optimized, and it would be several years before this method would find further uses (See Chapter 4).

Chapter 1-4 The type 2 tert-amino effect reaction



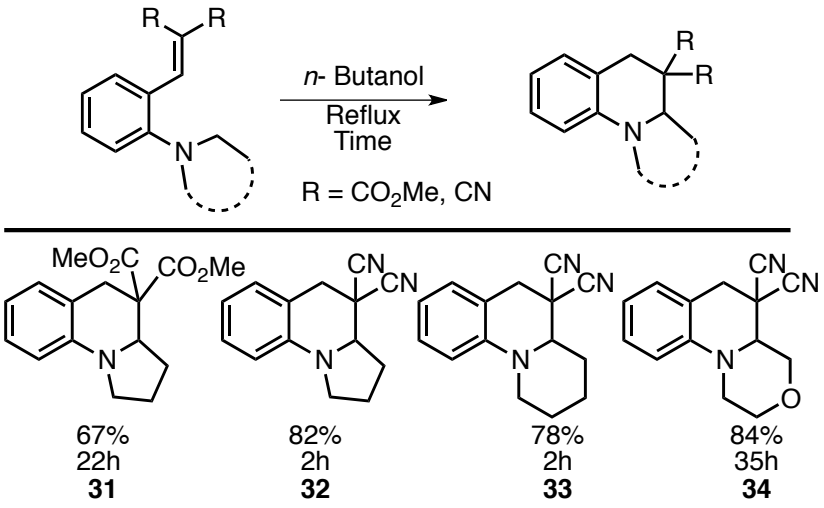
Scheme 1-4.1: First Known Type 2 Tert-Amino Effect Reactions



The tert-amino effect is not limited to the generation of 5-membered rings. When Cramer was reacting anilines with alloxan, he reported a different product when *o*-dimethylamino aniline was condensed with alloxan.[9] In 1969, Meth-Cohn confirmed that this side product was a 6-membered spirocycle, not the benzimidazole (Eq 1, Scheme 1-4.1).[9] To see if this reactivity was unique to alloxan, they treated *o*-dimethylamino aniline with N-methyl isatin, which is similar to alloxan in that both contain ketones that are

flanked by amides. When N-methyl isatin was allowed to react with the dimethyl aniline, only the imine product was observed (Eq 2). The authors next attempted the reaction with a pyrrolidine aniline (Eq 3), which produced a spirocyclic oxindole. They did not report a yield on this reaction, only that it had been formed. This showed that the synthesis of 6-membered rings by the tert-amino effect was possible. It also underscored the fact that heterocycles seem to be more reactive than dialkyl tertiary anilines. Reinhoudt and coworkers, in their investigations, further explored this effect in C–C bond forming reactions.

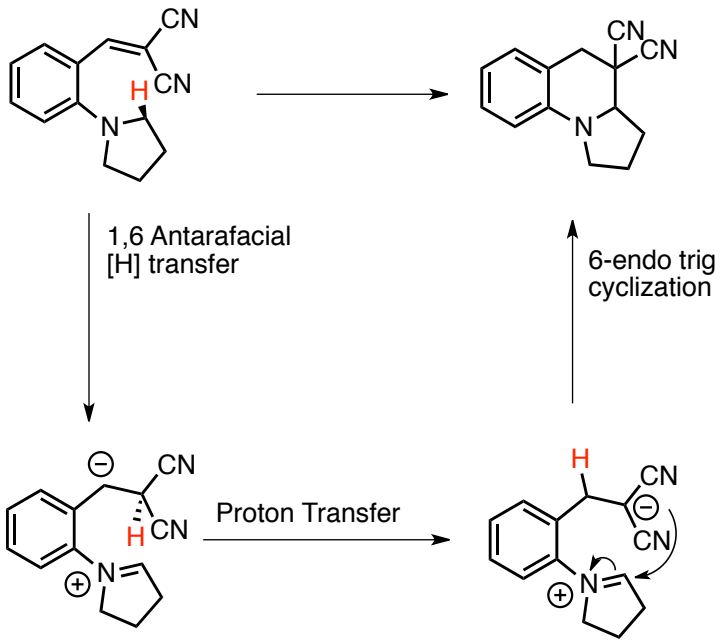
Scheme 1-4.2: Trends in the type 2 Tert-Amino Effect



While investigating the type1 tert-amino effect, Reinhoudt and coworkers also investigated the formation of six member rings (Scheme 1-4.2).[10] While molecules with an electron-withdrawing group on the α carbon gave 5-membered rings; molecules that contain two electron-withdrawing groups on the ß-carbon formed six membered rings. Molecules containing only one electron withdrawing group at the ß carbon did not undergo reaction. It was found that pyrrolidines **31-32** react the fastest and produce the highest yields . The ability of the electron withdrawing groups to stabilize an anion have

an effect on the reaction, as switching from a malonate **31** to the more electron deficient malononitrile **32** greatly improved yield and reaction time. Moving to larger rings on the tertiary amine gave a slightly reduced yield (**33**). Switching from a piperidine to a morpholine drastically increased the reaction time (**34**), likely due to the electron withdrawing oxygen present. This indicated that the ability of the amine to stabilize a cation is vital in much the same way the electron withdrawing groups are necessary. These findings, along with what is known about the type 1 tert-amino effect reaction lead Reinhoudt to propose a similar mechanism as seen for the formation of 5-membered rings (Scheme 1-4.3).

Scheme 1-4.3: Proposed Type 2 Mechanism

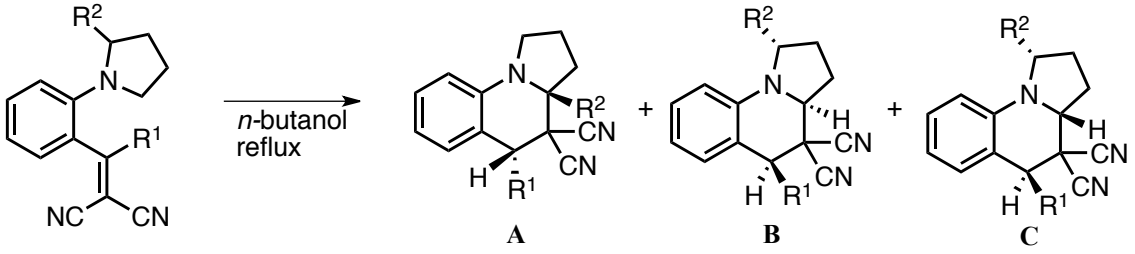


This included an antarfacial 1,6-[H] transfer as was seen in the type 1 reaction. Following this was a proton transfer from the electron-withdrawing group, forming a

stabilized anion. The ring formation occurs through a 6-endo-trig cyclization to produce the 6-membered ring. While this was a valid proposal for the mechanism, further exploration would lead to a re-evaluation of the mechanism.

One such study looked at the regioselectivity in these reactions (Table 1-4.1).[13] In it, Reinhoudt studied the effects of substituting the pyrrolidine ring as well as the α position of the double bond. When only a substituted pyrrolidine was used, the regioselectivity favored hydride transfer from the more substituted carbon attached to the nitrogen (Entries 2-3). Thus, when R^2 was a methyl group, the reaction exclusively gave one regioisomer. When R^2 was switched to a larger and less donating methoxy methyl substituent, the regioselectivity still favored forming the more substituted position, but with some of the other regioisomers made as well.

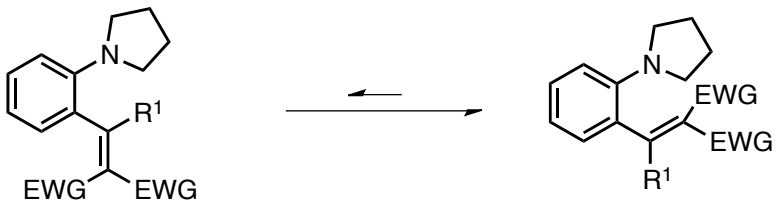
Table 1-4.1: Regioselectivity in the Type 2 Tert-Amino Effect.



Entry	R^1	R^2	Time (h)	Yield (%) **A**	**B**	**C**
1	H	H	2	82		
2	H	CH_3	2	85		
3	H	CH_2OCH_3	1.5	46	19	17
4	CH_3	H	5	79		
5	CH_3	CH_3	5	79		
6	CH_3	CH_2OCH_3	5	33	35	6
7	4-$C_6H_4CH_3$	H	72	86		
8	4-$C_6H_4CH_3$	CH_3	72	76	13	9
9	4-$C_6H_4CH_3$	CH_2OCH_3	72	16	41	15

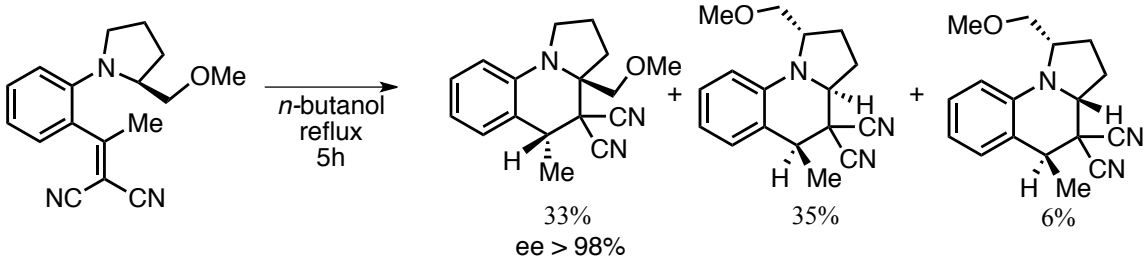
The observed regioselectivity can be explained by the higher likelihood of the hydride shift occurring from the position that would form the more stable cation. There seems to be a limit to this trend; a large R^2 group will provide the less substituted isomer though this could be due to sterics or the electron withdrawing nature of methoxy methyl group (Entries 3, 6, and 9). There is also a correlation between size of R^1 group and the rate of the reaction. There is a drastic decrease in rate as the size of R^1 increases. This would seem counterintuitive if the reaction began with a 1,6-[H] shift. A large R^1 group would force the ß-carbon closer to the migrating hydride (Figure 1-4.1), which would increase the reaction rate. Furthermore, the proposed mechanism could not explain why such high diastereoselectivity is observed when R^1 and $R^2 \neq$H.

Figure 1-4.1: Effect of large R^1 group



There was also a unique occurrence observed when an optically pure starting material was subjected to these reaction conditions (Scheme 1-4.4).[14] When optically pure proline derivative **35** was subjected to refluxing butanol, three products were reported.

Scheme 1-4.4: Retention of Stereochemistry



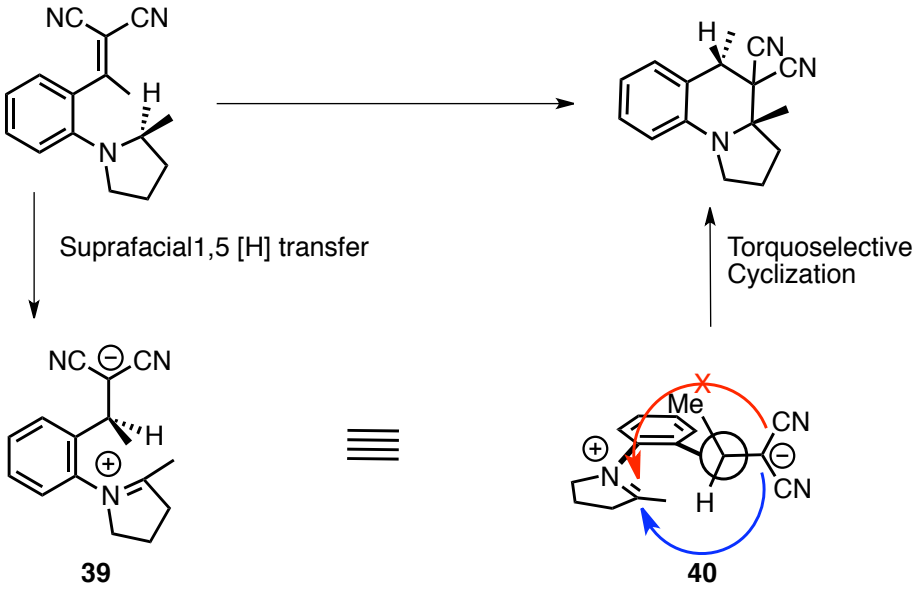
33%
ee > 98%

35% 6%

35 **36** **37** **38**

The products of hydride transfer from the less substituted side of the amine **37** and **38** could be rationalized as being diastereoselective based on the preexisting stereocenter. What was more shocking was that the product of hydride transfer from the more substituted side **36** was obtained in high ee and as a single diastereomer. In order to account for this retention of stereochemistry, Reinhoudt had to revise the mechanism of this type of tert-amino effect (Scheme 1-4.5).

Scheme 1-4.5: Revised Mechanism for Type 2

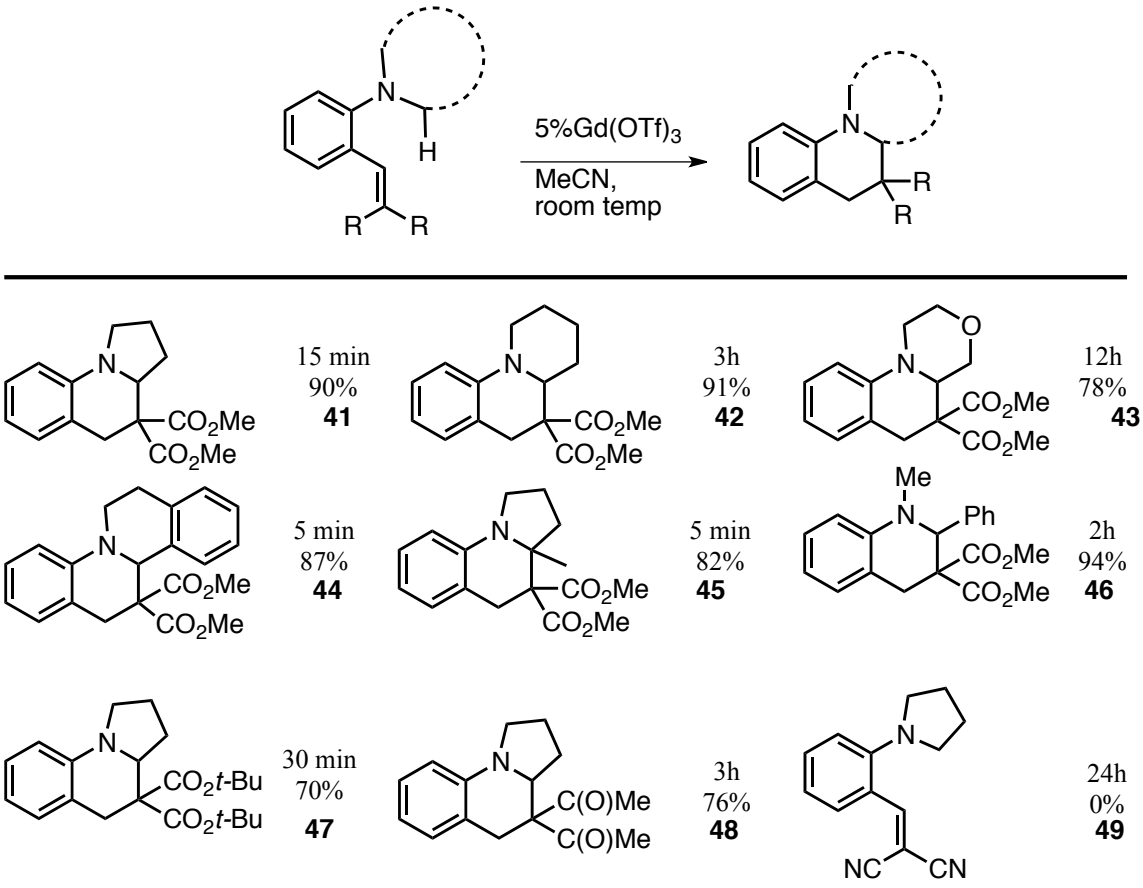


The reaction begins with a 1,5-hydride shift. This shift is suprafacial, meaning the hydride transferred ends up on the same face of the molecule it was on initially. This forms a new stereocenter at the α carbon, as well as a tertiary cation stabilized by an amine and a malononitrile stabilized anion **39**. At this point the molecule must now undergo 6 endo trig cyclization, but can rotate in one of two directions **40**. Counterclockwise rotation requires the two methyl groups to pass by each other, while clockwise rotation forces the much smaller hydrogen to pass the methyl group. This steric repulsion makes the reaction torquoselective to produce the observed diasteromer. This combined with suprafacial hydride transfer allows for the self-regeneration of the stereocenter in the type 2 tert-amino effect reaction.

Two of the key limitations of the type 2 tert-amino effect were that it required long reaction times at high temperatures and that it works best with malononitriles, which limit the possible scope. In 2009, Seidel and coworkers developed a low temperature

reaction by using $Gd(OTf)_3$ to catalyzed the type 2 tert-amino effect cyclization (Table 1-4.2).[15]

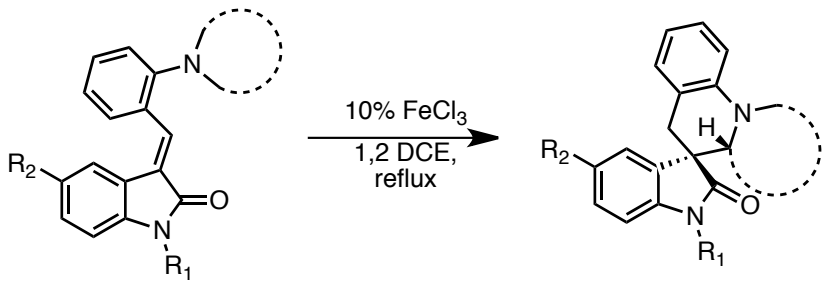
Table 1-4.2: Room Temperature Type 2 Reactions

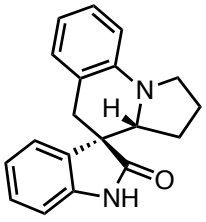
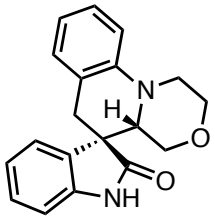
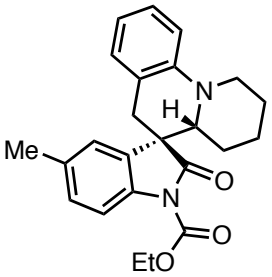
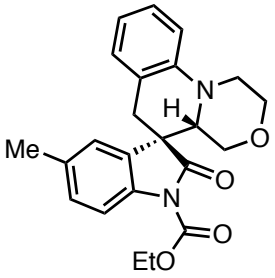
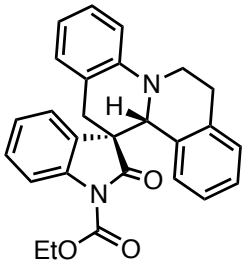
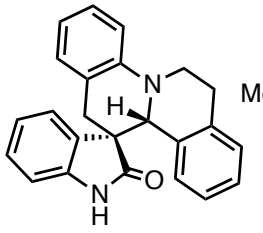
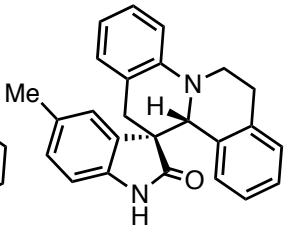
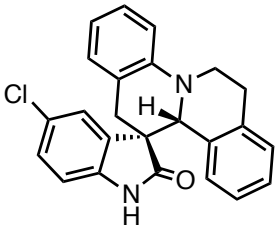


Instead of malononitriles, malonates were used. Typical trends were observed where the 5 membered pyrrolidine reacts faster than the piperidine and the morpholine **41-43**, though all react in much less time than would be expected for a purely thermal reaction. Even when catalyzed by a Lewis acid, the hydride transfers from the more substituted position, be it a tetrahydroisoquinoline **44** or a methyl pyrrolidine **45**. When an acyclic tertiary amine was used, the hydride transferred from the benzyl position rather than the methyl position **46**. Larger malonates **47** and ketones **48** were also reactive under

these conditions. Ironically, the one substrate that did not react with the Lewis acid was the malononitrile **49**, likely due to the inability of the nitriles to chelate the Lewis acid.

Table 1-4.3: Type 2 with Isatin Derivatives

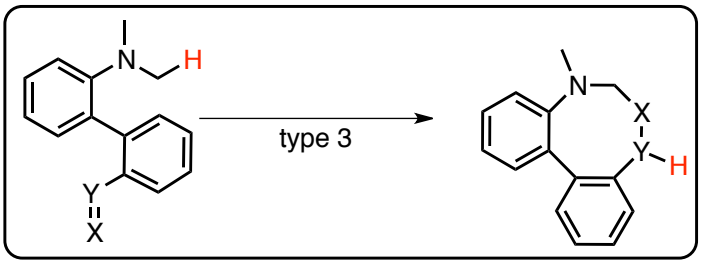


			
5h 97:3 96% **50**	72h 99:1 97% **51**	3h 86:14 92% **52**	10h 86:14 93% **53**
			
1h 91:9 89% **54**	20 min 90:10 95% **55**	30 min 91:9 97% **56**	5 min 91:9 94% **57**

The type 2 tert-amino effect has seen a resurgence in recent years.[16] One of the more interesting uses of this reactivity was by Yuan to synthesize highly substituted spirocycles from isatin derivatives using an iron catalyst (Table 1-4.3).[17] These stand out

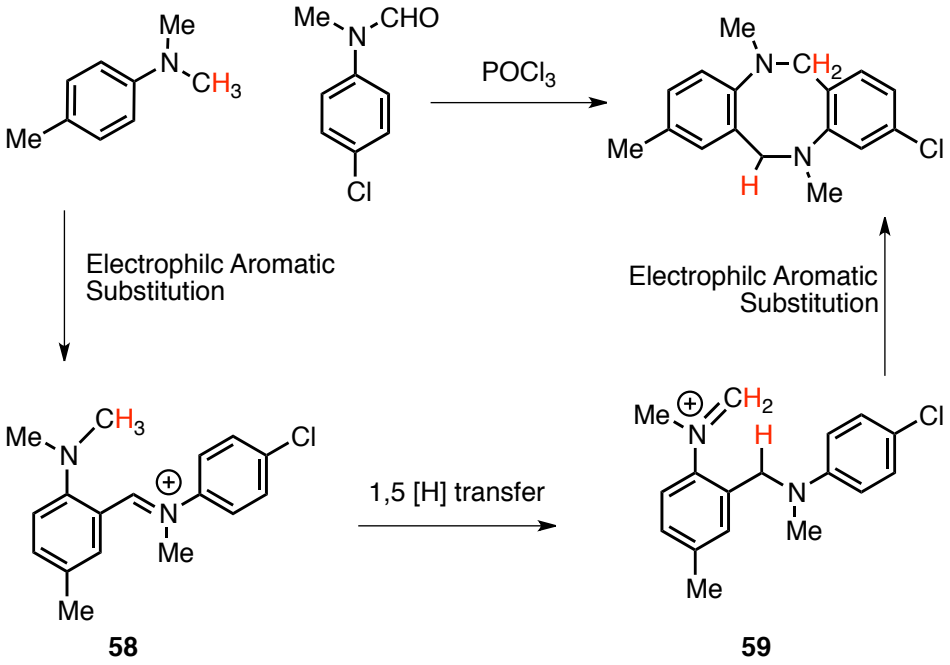
for two reasons. One is that they are the first use of isatin derivatives in a type 2 tert-amino effect since Meth-Cohn in 1969. Second is that the starting materials only posses one electron withdrawing group where as all other known reactions have two. The reactions yield highly congested adjacent stereocenters in high yields and good diastereoselectivites. It is worth noting that the tetrahydroisoquinolines **54-57** react remarkably faster than any heterocycle that does not contain a benzylic C–H donor. This is a unique and efficient way to make very diverse spirocycles using the type 2 tert-amino effect.

Chapter 1-5 The type 3 tert-amino effect



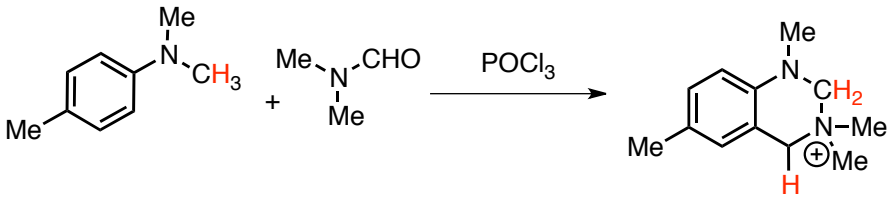
The type 3 tert-amino effect is not as rigorously investigated as the previous types. It is defined as any reaction that produces a ring larger than six. Meth-Cohn described one of the first known type 3 reactions when carrying out a Vilsmeier-Haack reaction with tertiary formamides (Scheme 1-5.1).[18]

Scheme 1-5.1: Type 3 Tert-Amino Effect Reactions



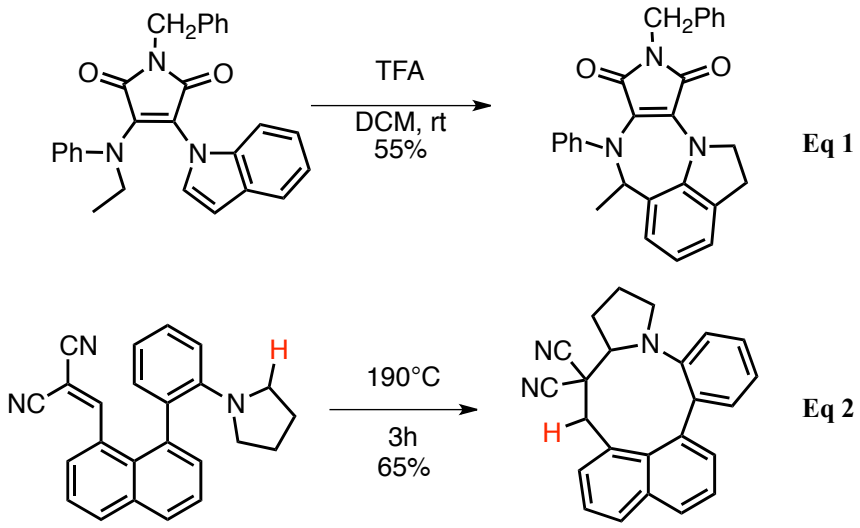
The reaction begins through typical Vilsmeier-Haack conditions to form an iminium ortho to the tertiary amine through electrophilic aromatic substitution **58**. This intermediate then undergoes a 1,5-[H] shift similar to that observed in the type 2 reactions. This intermediate **59** can only attack the iminium through an intramolecular electrophilic aromatic substitution. If the reaction is carried out under standard Vilsmeier-Haack conditions (using DMF and $POCl_3$), a six membered ring is formed with quaternary ammonium (Scheme 1-5.2) Also if the formamide is not tertiary, it will form a six membered product with the loss of a proton.[19]

Scheme 1-5.2: Vilsmeier Haack Type 2



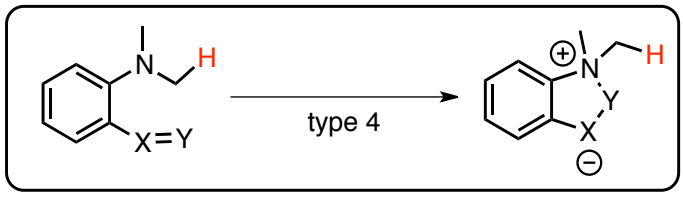
Other type 3 reactions go through different mechanisms, but all yield large rings. Preobrazhenskaya and coworkers have shown maleimides with indole groups will undergo cyclization while also reducing the indole to an indoline (Eq 1, Scheme 1-5.3).[20]

Scheme 1-5.3: Other Type 3 Reactions



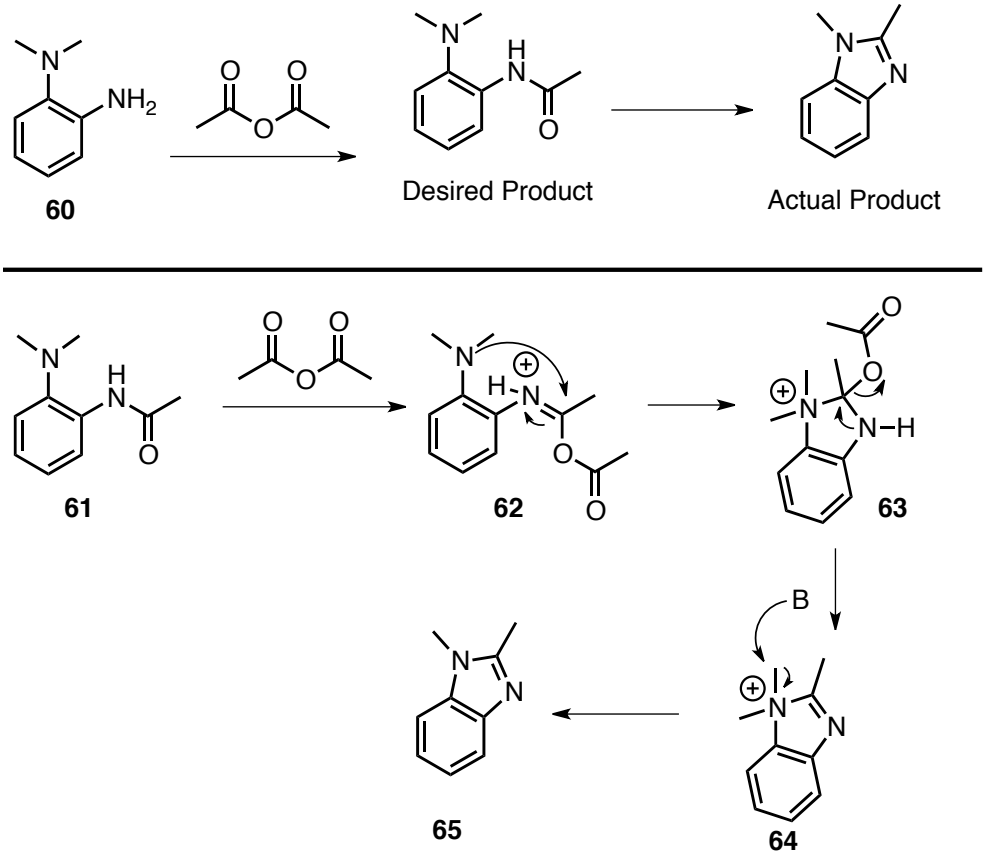
This cyclization also goes through an intramolecular electrophilic aromatic substitution. This is not necessary for all type 3 reactions. Mátyus and coworkers recently published the synthesis of large rings (Eq 2).[21] This reaction is similar to a type 2 tert-amino effect, but it occurs through a larger conjugated system. The reaction is not as simple as most type 2 reactions. Heating for extended periods in polar solvents did not lead to reaction, nor did microwave irradiation. It was only when an ionic liquid was used as the solvent that the reaction occurred. The mechanism of this reaction also speaks to the ambiguity to the type 3 tert-amino effect. Since there is no standard for what mechanism it proceeds by, Mátyus defines these reactions as an extended type 2 reaction, yet by the definition set out by Meth-Cohn and several groups, this reaction falls into type 3.

Chapter 1-6 The type 4 tert-amino effect



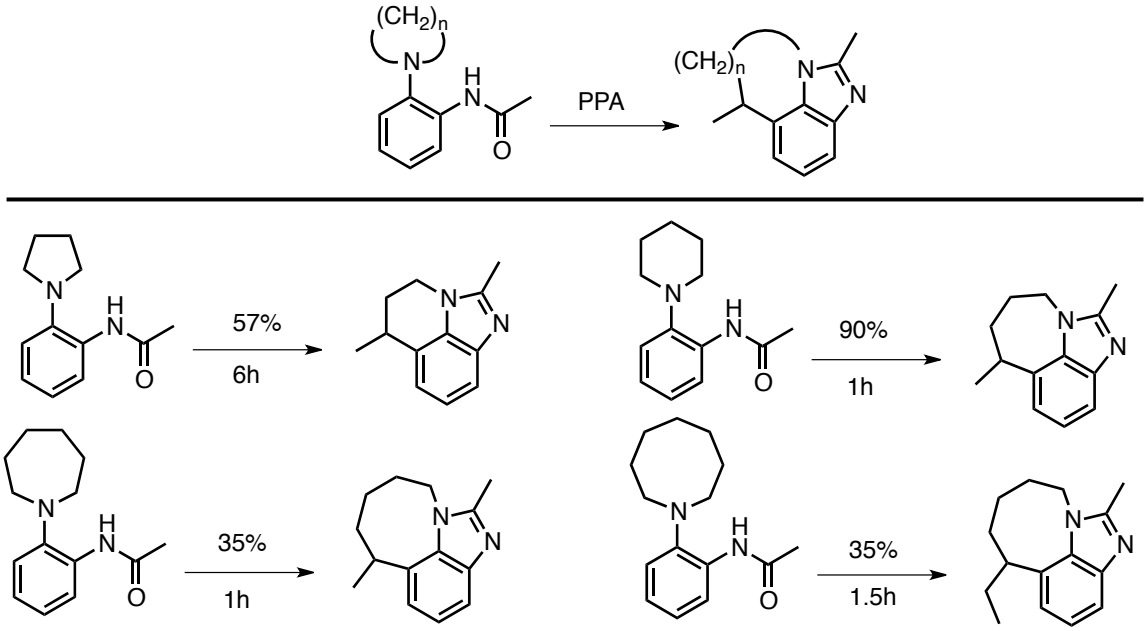
The type 4 tert-amino effect was the first tert-amino effect reaction to be discovered, and was reported in 1895.[22] As with many other tert-amino effect reactions, it was discovered by accident when trying to acetylate *o*-dimethylamino aniline (**60**, Scheme 1-6.1) using acetic anhydride. Instead of the desired product, a benzimidazole was produced. This was thought to come from initial acetylation of the starting material **61**. The resulting amide then reacts with another equivalent of acetic anhydride to form an acylated iminium **62**. What occurs next is what engenders this reaction a type 4 tert-amino effect reaction. Instead of a hydride transferring, the tertiary nitrogen attacks the iminium to generate a quaternary ammonium **63**. The reaction then undergoes aromatization and demethylation to produce a benzimidazole (65). This example highlights the key part of any type 4 reaction. The nitrogen attacks the ortho group rather than a hydride attacking the ortho group. By definition, a four or a five membered ring could be formed, yet all known reactions form 5-membered rings. The fate of the group on the tertiary amine is unique and can be different based on the reaction conditions.

Scheme 1-6.1: First Known Tert-Amino Effect Reaction



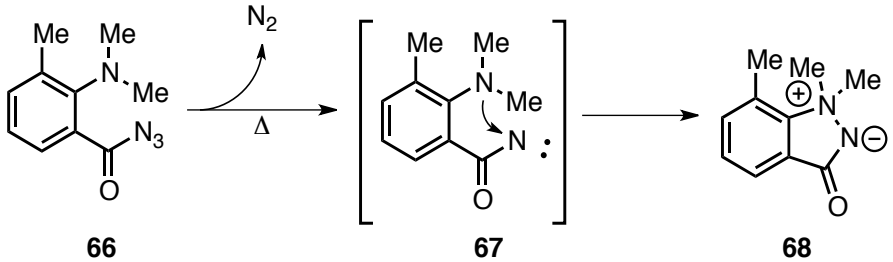
In the previous example, a base removes the methyl group. In reactions where the alkyl group is a ring (Table 1-6.1),[23] the quaternary ammonium undergoes a different reactivity. In the presence of polyphosphoric acid, the ammonium undergoes Hoffman-type elimination to give tethered alkenes, which in the presence of a strong acid,

Table 1-6.1: Type 4 Reactions with Polyphsphoric Acid



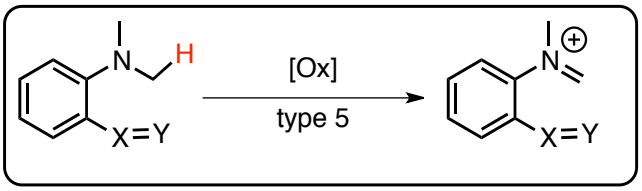
undergo electrophilic aromatic substitution to afford tri-cyclic products. There are also cases where the ammonium is stable and can be isolated, such as when an acyl azide **66** (Scheme 1-6.2) undergoes a type 4 tert- amino effect reaction.[24] Upon heating, the azide decomposes to nitrogen gas and a nitrene. Rather than undergo the predicted Curtius rearrangement, the tertiary nitrogen intercepts the nitrene to form a stable ylide **68**.

Scheme 1-6.2: Nitrene Interception via type 4



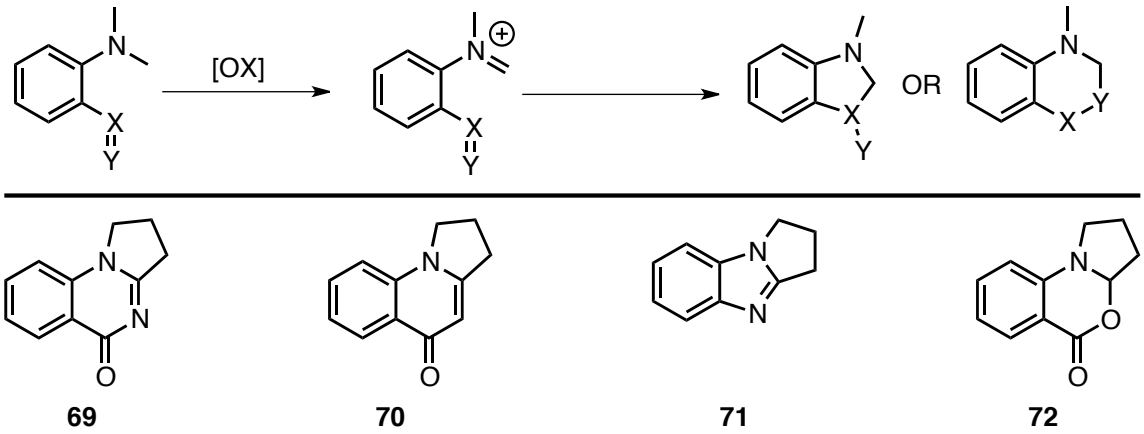
66 **67** **68**

Chapter 1-7 The type 5 tert-amino effect reaction



The type 5 tert-amino effect is unique among tert-amino effects because it is the only one that requires a stoichiometric amount of oxidant. The oxidant forms an iminium (or an iminium radical), which then undergoes reaction with the nucleophilic group at the ortho position (Scheme 1-7.1).[25]

Scheme 1-7.1: General Scheme for Type 5 Reactions



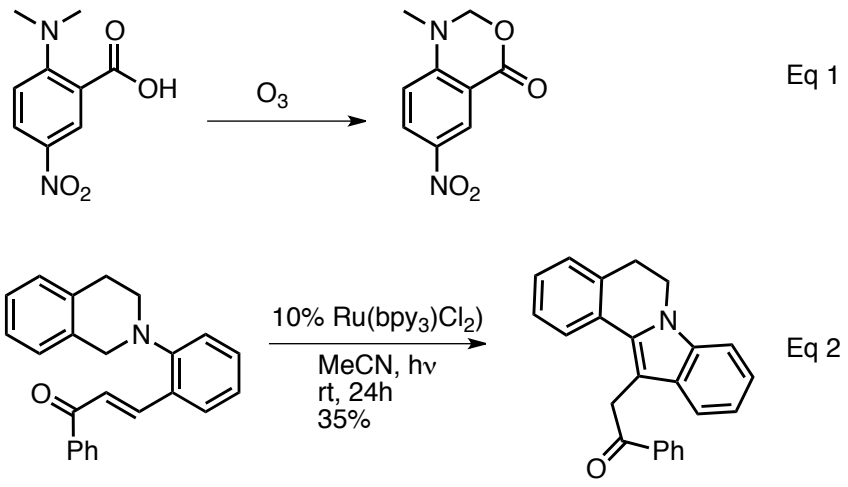
69 **70** **71** **72**

The methodology can produce lactams **69**, enones **70**, benzimidazoles **71** and lactones **72**. While typical oxidants are metals such as Hg^{II} or MnO_2, less traditional oxidants have been utilized to form the iminium. (Scheme 1-7.2).

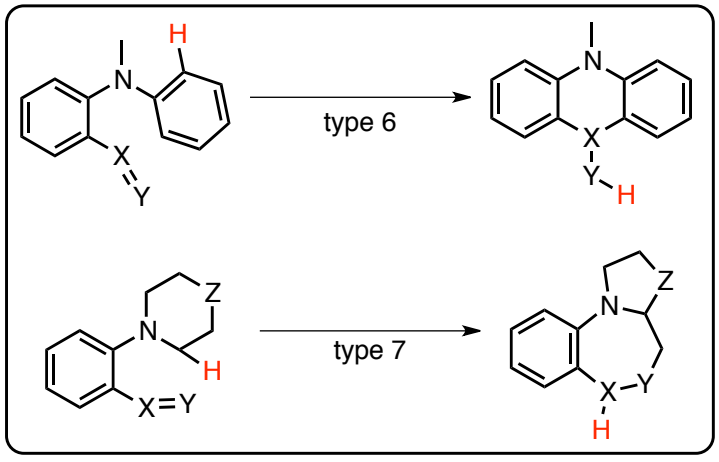
When ozone is used (Eq 1),[26] it oxidizes amine forming an iminium resulting in formation of a lactone while producing only water and oxygen as byproducts. More

recently, Reiser and coworkers have shown that a photocatalyst can be used to form indoles from tetrahydroisoquinolines (Eq 2).[27] Both of these methods circumvent the inherent weakness of the type 5 tert-amino effect, the use and removal of the byproduct of a stoichiometric amount of oxidant.

Scheme 1-7.2: Type 5 Using Non-Traditional Oxidants

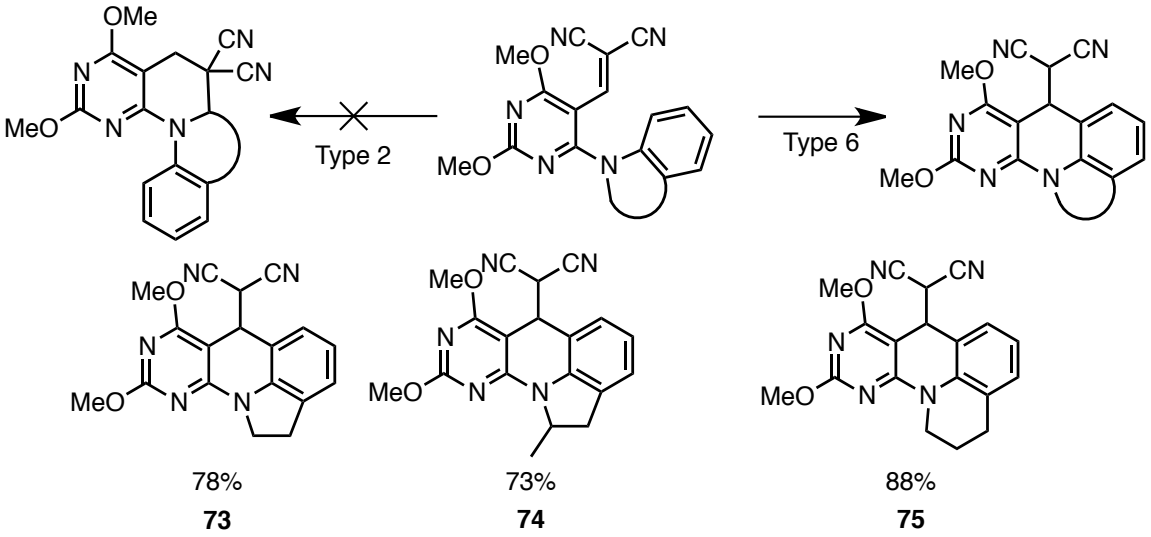


Chapter 1-8 The type 6 and type 7 tert-amino effect reactions



The Type 6 and 7 tert-amino effect reactions are not nearly as well studied as types 1-5. These reactions could be considered variations of type 2 reactions.

Scheme 1-8.1: Type 6 Tert-Amino Effect Reactions

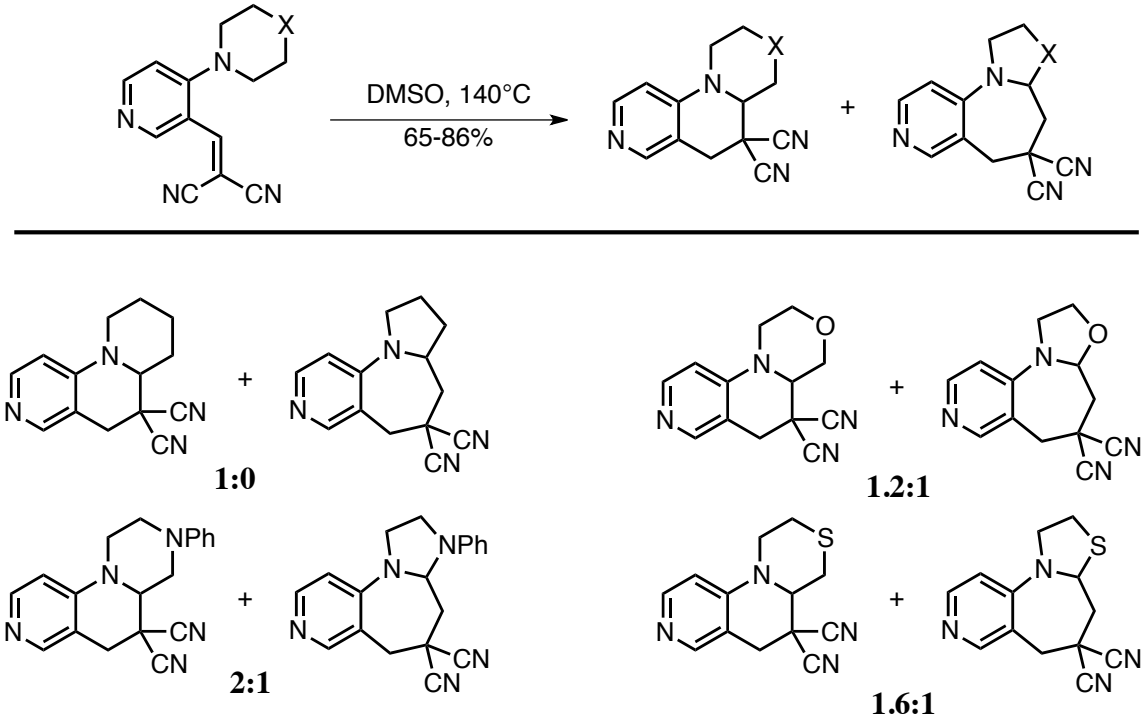


When some cyclic anilines are heated, rather than the predicted type 2 cyclizations, a different cyclization was observed (Scheme 1-8.1).[28] In lieu of the hydride transfer reaction, the aniline had undergone electrophilic aromatic substitution. This was found to be the primary reactivity for both indolines **73-74** and tetrahydroquinolines **75**. The phenyl group must be attached to the nitrogen, as benzyl amines underwent type 2 reactions. This reactivity is similar to that observed for type 3 reaction, yet it only yields a 6-membered ring, so it can not be categorized as a type 3. While it is not known if it is necessary for the reaction to take place, all reported type 6 reactions occur on substrates containing a pyridine ring.

The type 7 tert-amino effect is unique in that there is only one report of it occurring, yet this reaction has its own classification.[29] In a type 7 reaction, the tertiary

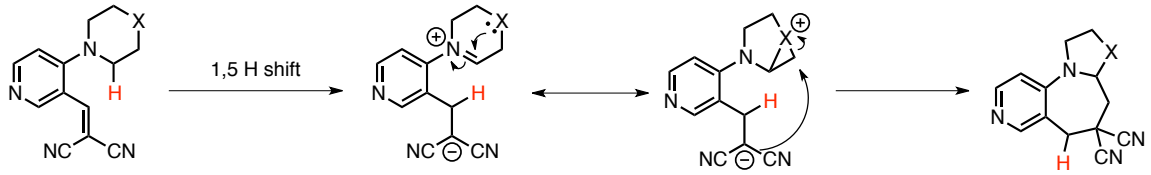
amine is a six membered ring. Upon heating, it should undergo a type 2 reaction to form a 6,6,6 fused ring system, but also forms a 6,7,5 ring system (Scheme 1-8.2).

Scheme 1-8.2: Type 7 Tert-Amino Effect Reaction



In order for this isomerization to occur, the ring must contain a heteroatom; a piperidine moiety only undergoes type 2 cyclization, while the morpholine analog yielded a nearly equal mixture of the two products. Piperazine produced a 2:1 ratio in favor the type 2 product, and thiomorpholine formed the products as a mixture as well. This reactivity seems to be unique to molecules with the pyridine linker, as none of the type 7 reaction product was reported in cases where a non-pyridine linker was used. The reaction can be envisioned to proceed from a typical type 2 reaction (Scheme 1-8.3). The heteroatom then attacks the iminium, forming a three membered ring. The anion can then attack either carbon of the three membered ring, one of which produce the type 2 product and the other of which will form the type 7 product,

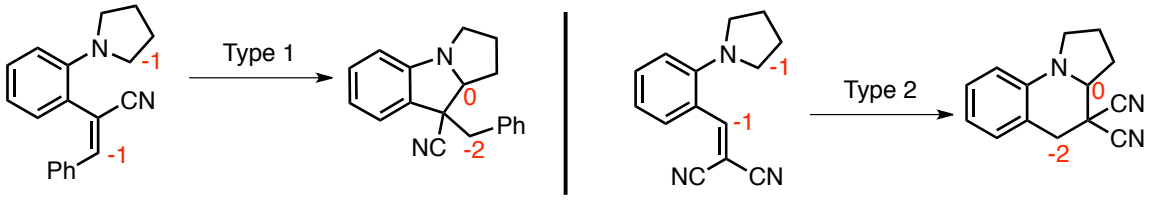
Scheme 1-8.3: Mechanism for type 7 reactions



Chapter 1-9 The Tert-amino Effect and Redox neutral reactions

The tert-amino effect is of significance, not just because it is capable of forming new carbon-carbon and carbon-heteroatom bonds, but also because these bonds are formed in a redox neutral manner. In any reaction that uses the tert-amino effect (with the exception of type 5), the oxidation states for two carbons change, one gets oxidized and the other gets reduced (Scheme 1-9.1).

Scheme 1-9.1: Redox Neutral Tert-Amino Effect Reactions



This disporportionation occurs without any external oxidant or reductant. Since no extra reagent has to be added, there is no difficult workup to remove oxidants or reductants. Reactions that can form C–C or C–Het bonds while avoiding stoichiometric byproducts are of great interest to the organic chemist. While the tert-amino effect is one of the oldest known redox neutral reactions, new redox neutral methods are being developed. Following is an account of my research into such redox neural processes to form aromatic pyrroles and indoles.

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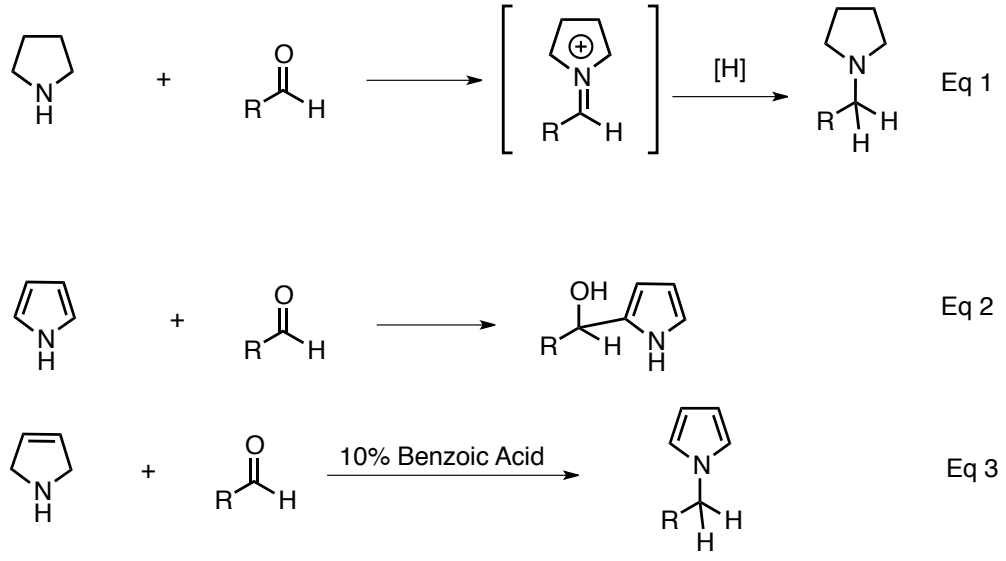
Chapter 2-1 Redox amination

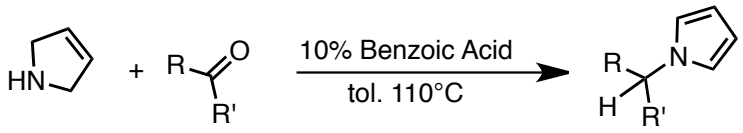
One of the most common synthetic methods for the formation of carbon-nitrogen bonds is reductive amination (Scheme 2-1.1, Eq 1). In Redox amination, an amine is allowed to react with a carbonyl compound and the intermediate imine or iminium is then reduced using a stoichiometric amount of reductant. While commonly used in organic synthesis, this method is not without its shortfalls. On top of requiring a stoichiometric amount of reductant, it is not compatible with aromatic heterocycles such as pyrroles and indoles, which undergo nucleophilic attack of the carbonyl at the 2 and 3 positions of the aromatic heterocycle, respectively (Scheme 2-1.1, Eq 2). If one wishes to make an aromatic N-substituted heterocycle, one must first use a non-aromatic precursor of the desired heterocycle for reductive amination, followed by oxidation to the aromatic heterocycle. In 2009, our group published a strategy to synthesize pyrroles via a pro-aromatic pyrroline using redox amination, a redox neutral method of forming C–N bonds (Eq 3).[1]

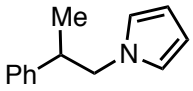
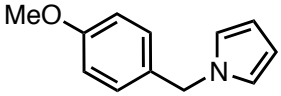
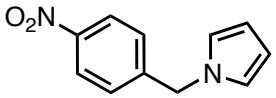
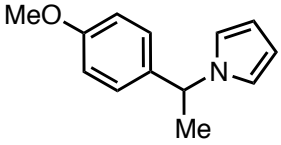
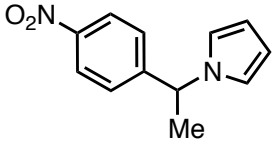
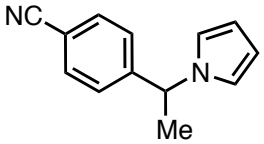
Scheme 2-1.1: Reductive amminations



In the aforementioned redox amination, pyrroline is combined with an aldehyde or ketone in the presence of benzoic acid. In the process, both a new carbon nitrogen bond is formed and the pro-aromatic pyrroline is oxidized to a pyrrole. No external oxidant or reductant is needed, making this reaction redox neutral. The reaction is applicable to a broad range of aldehydes and ketones (Table 2-1.1).

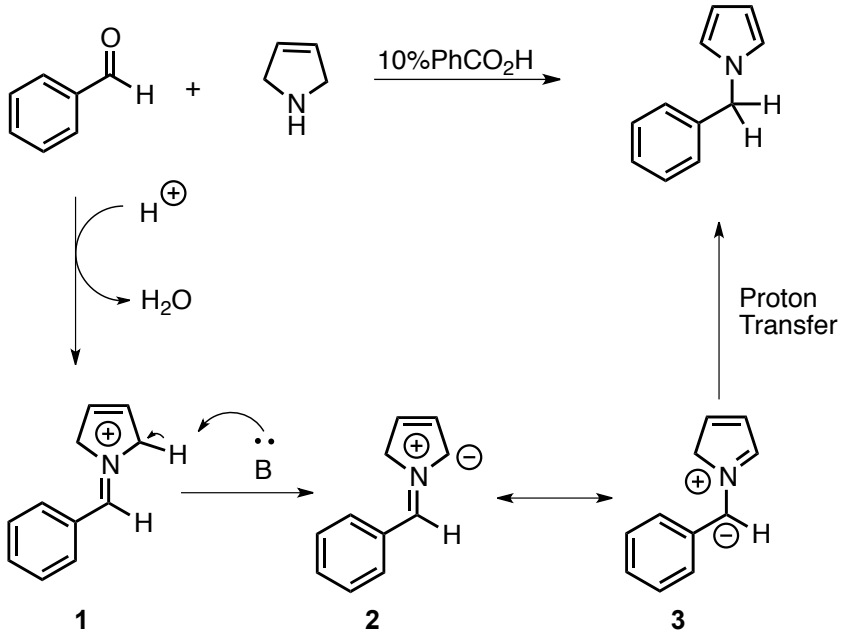
Table 2-1.1: Redox Aminations using Pyrroline



Entry	Product	Yield	Time (hours)
1		88%	12
2		85%	5
3		94%	4
4		65%	12
5		90%	8
6		93%	12

Redox amination proceeds efficiently with both aliphatic (Entry 1) and aromatic aldehydes (Entries 2 and 3). There does not appear to be much difference in reactivity of aromatic carbonyl compounds that bear electron withdrawing (Entry 3) or electron donating groups (Entry 4), though there is a more substantial difference with aromatic ketones. The ketones required much longer reaction times than did the aldehydes (Entries 4-6). While electron withdrawing ketones give high yields, there is a drastic reduction in yield between anisaldehyde (Entry 2) and acetanisole (Entry 4). The lower yield and longer reaction time for the acetanisole a can be rationalized if the reaction goes through a zwitterionic intermediate (Scheme 2-1.2).

Scheme 2-1.2: Redox Amination Mechanism

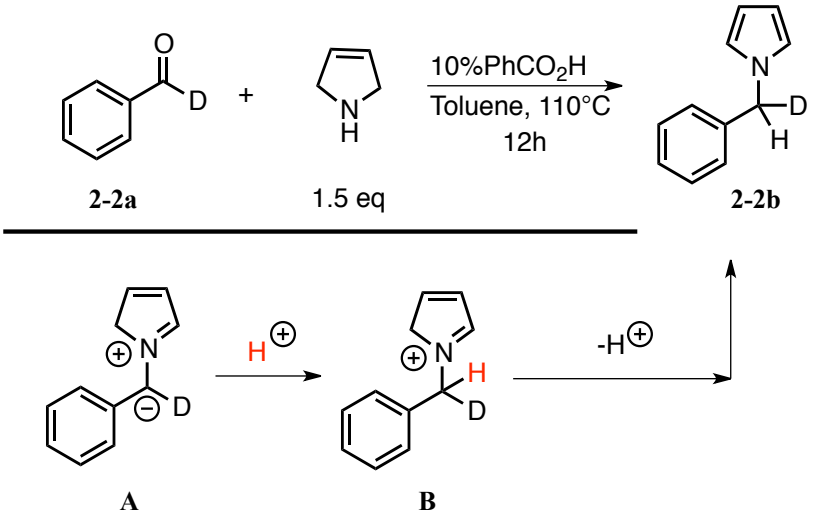


Upon acid catalysis, pyrroline condenses with the carbonyl to give intermediate iminium **1.** Next, a base deprotonates the iminium, forming an azomethine ylide **2**, which is in resonance with **3**. The anion at the benzyl position on **3** will be stabilized by electron withdrawing groups and destabilized by electron donating groups. This could be why

electron withdrawing acetophenone react faster and in higher yield than the corresponding electron donating acetophenone. Proton transfer, either intra or inter molecular, gives the desired N-substituted pyrrole.[2] These initial studies of redox amination showed that it is a versatile methodology, which deserves further studies.

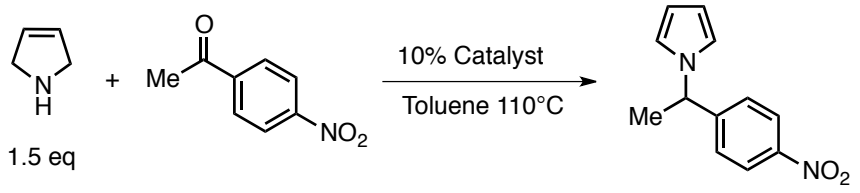
Chapter 2-2 Attempts at enantioselectivity

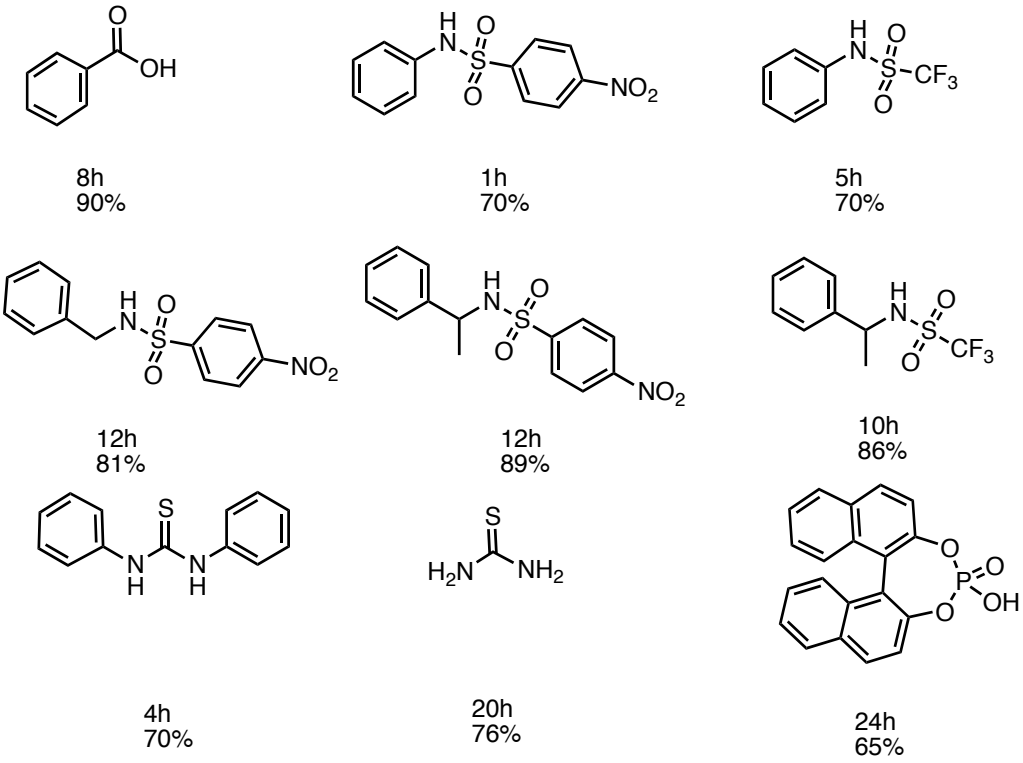
Scheme 2-2.1: Deuterium Labeling Study



Since it had been shown that reodx amination allows for the formation of stereogenic centers when pyrroline reacts with acetophenones, the task of developing an enantioselective variant of this redox amination was undertaken. The first step to do this was to explore the mechanism of this reaction. To do this, we carried out the redox amination of deuterated benzaldehyde with pyrroline (Scheme 2-2.1). The N-benzyl pyrrole product (2-2b) was formed with complete retention of deuterium at the benzyl position, indicating that once protonation of the azomethine ylide **A** occurs, it is not reversible. It was hypothesized that if one controlled the face from which protonation occurred, an enantioselective variant of the redox amination could be achieved.

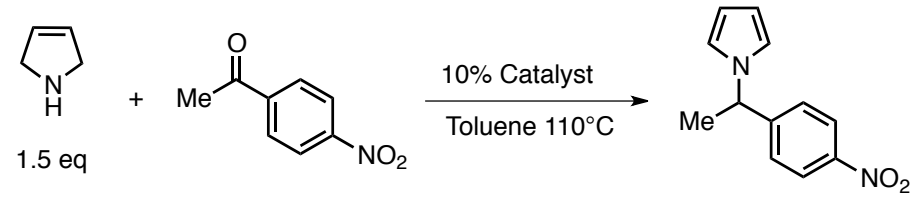
Table 2-2.1: Redox amination catalyst screening



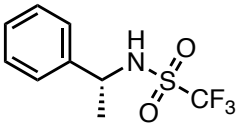
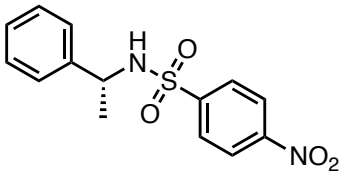
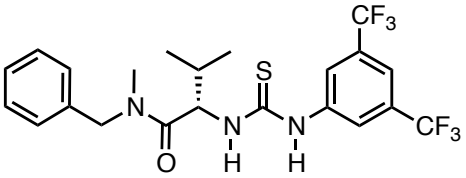
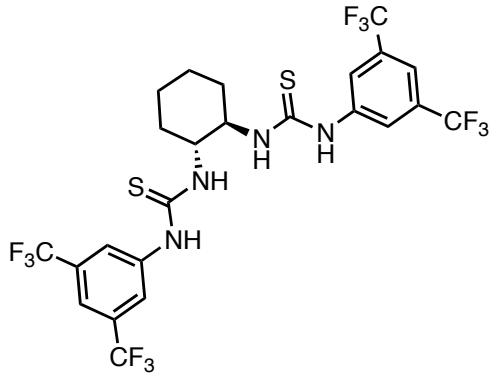
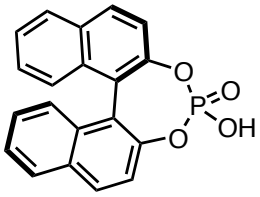


We chose to screen a range of possible catalysts that could lead to an enantioselective reaction using 4-nitroacetophenone as our substrate . We discovered redox amination could be catalyzed by a range of different molecules including carboxylic acids, phosphoric acids, sulfonamides, and thioureas (Table 2-2.1). With a wide range of catalysts able to promote this reaction, we then explored this redox amination with a series of enantiopure chiral catalysts (Table 2-2.2). While all catalysts screened did produce the desired pyrrole, no appreciable enantioselectivity was observed.

Table 2-2.2: Unsuccessful Chiral Catalysts



ee = 0[a]

	Yield		Yield
	63%		81%
	71%		76%
	62%		

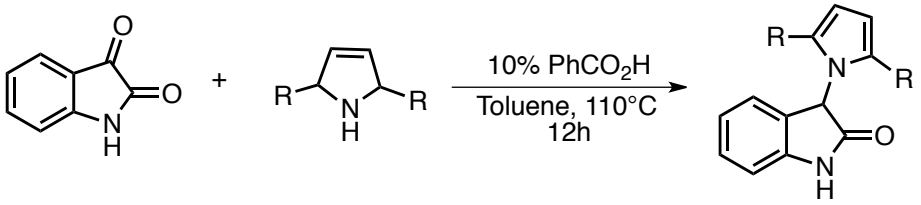
[a] ee determined by chiral HPLC

At this point we decided to rethink our choice of 4-nitroacetophenone for optimization. While chosen for its previously shown efficiency in redox aminations, it was not ideal for an enantioselective variant of this reaction. It was theorized that the redox amination of acetophenones competes with formation of an enamine. To prevent this side product,[3] we sought a ketone that would be unable to form an enamine, but would form a chiral center upon redox amination.

Chapter 2-3 Redox aminations with isatin

We sought a ketone that would be both unable to form an enamine and would yield a chiral product upon redox amination. Isatin (indolin-2,3-dione) was our ideal choice, based upon its commercial availability and established utility in organic synthesis.[4] The ketone carbonyl is flanked on one side by a phenyl group and on the other side by an amide carbonyl. These flanking groups make it impossible for an imine to isomerize to an enamine, and the fact that they are not equivalent means any product formed from the redox amination at the ketone will be chiral. We were excited to see that isatin and pyrroline cleanly reacted under previously established redox amination conditions to give 3-(1H-pyrrol-1-yl)indolin-2-one in high yield (Scheme 2-3.1).

Scheme 2-3.1: Redox aminations with isatin



Isatin 1.5 eq **2-3a** R=H 84%
2-3b R=Me 65%

While synthesis of these indolinones from pyrroline is unprecedented, it has previously been synthesized from 4-hydroxy proline by several different groups using a number of different conditions (Scheme 2-2.3).[5] While 4 hyrdroxy proline is preferable to pyrroline due to its availability from natural sources and its stability, it is limited to only making pyrrole, while pyrroline derivatives would easily allow for the synthesis of more diverse substituted pyrroles. This was demonstrated with the redox amination of 2,5

dimethyl pyrroline with isatin to obtain the dimethyl pyrrole (Scheme 2-3.1, 2-3b). This result was particularly encouraging given that dimethyl pyrroline had previously been shown to react exclusively with aldehydes and not ketones. This indicated that isatin could undergo redox aminations with amines that are unreactive with simple ketones. such as indoline.

Scheme 2-3.2: Redox aminations of 4-hydroxy proline

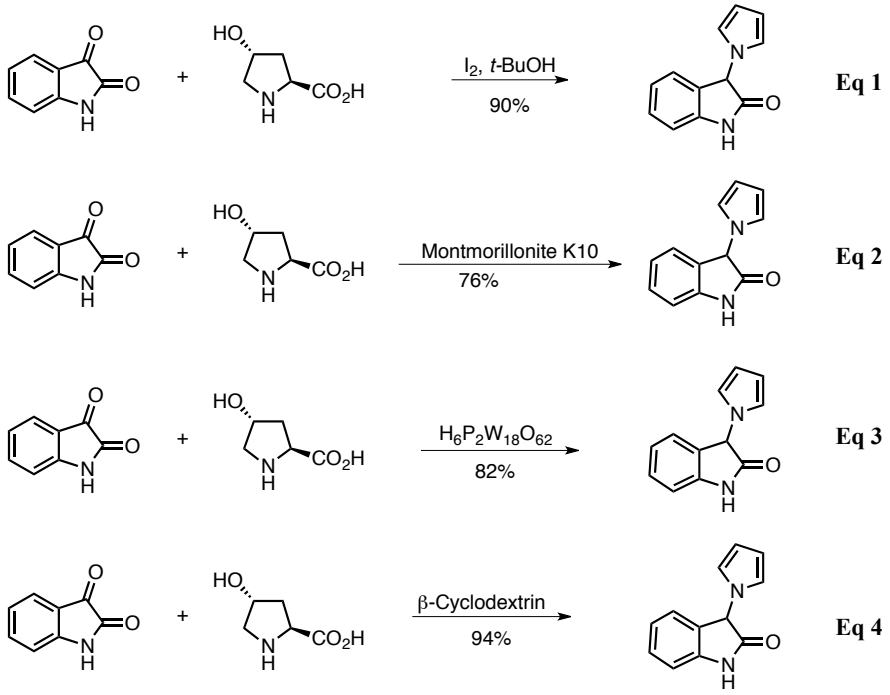
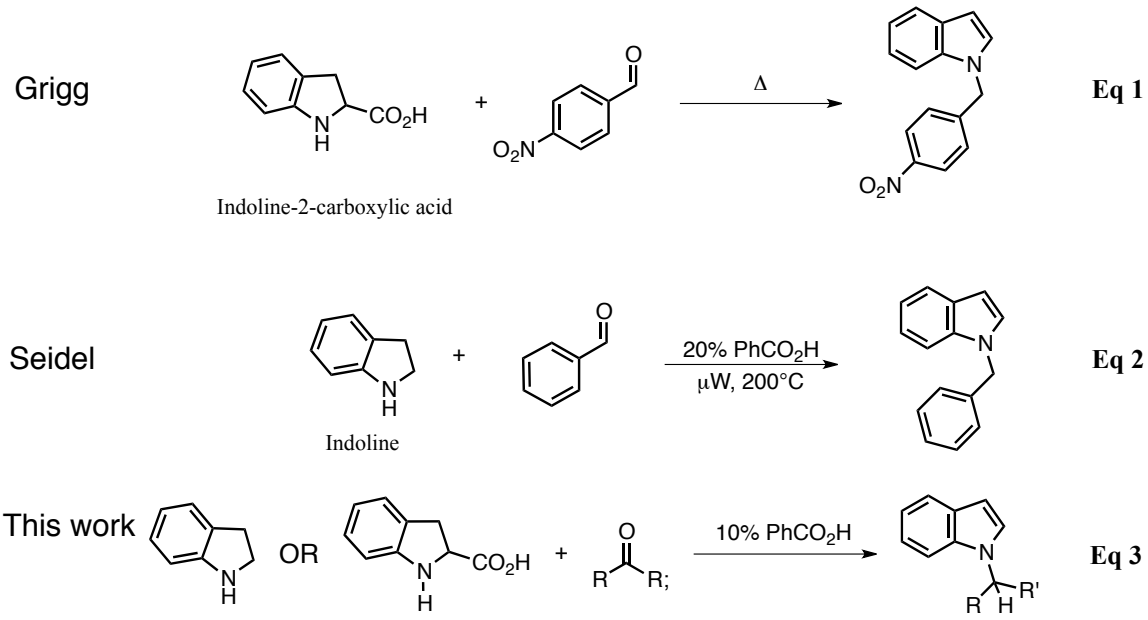


Figure 2-3.1: Redox Amination using Isatins



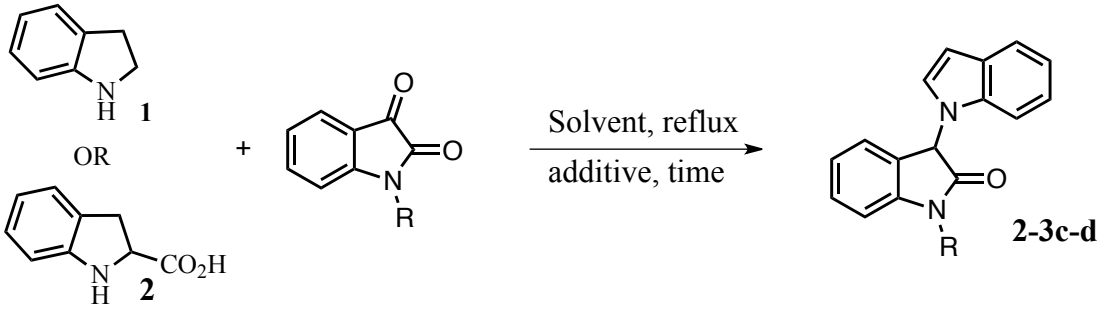
Indoline can be considered the pro-aromatic version of indole, much as pyrroline can be considered the pro-aromatic version of pyrrole. While pyrroline is a secondary amine, indoline is a secondary aniline, which is much less nucleophilic. Further, pyrroline is not aromatic, while indoline already contains an aromatic ring and thus does not experience as much energetic gain from becoming aromatic as pyrroline does.[6] For these reasons redox amination using indoline is not heavily explored in literature. There have been several recent publications reacting indoline with aldehydes to form indoles via redox amination. In 1984, Grigg and coworkers discovered by accident that indoline-2-carboxylic acid undergoes redox amination with aldehydes via decarboxylation of the iminium to form an azomethine ylide, which then undergoes proton transfer to give the aromatic indole (Figure 2-2,1, Eq 1).[7] They were trying to trap the azomethine ylide via a 3+2 reaction with dipolariphiles, yet the aromatic product was produced instead of the cycloaddition reaction. More recently, Siedel and coworkers have shown that indoline

undergoes redox amination with aldehydes under microwave conditions (Eq 2).[8] These results demonstrated that either indoline or indoline 2-carboxylic acid could be used to generate the desired indole, yet both only worked with aldehydes and no results with ketones were reported. With these results in mind, we set about exploring redox amination of isatins and indoline or indoline 2 carboxylic acid (Eq 3).

Chapter 2-4 Redox Aminations of isatins and indolines

The fact that indoline and indoline 2-carboxylic acid could be used presented several options. Redox amination with indoline would be more atom economical, yet indoline is a somewhat pungent liquid that can undergo oxidation to indole upon exposure to air for long periods of time. Indoline 2 carboxylic acid would have to undergo decarboxylation to give the desired product, but is air stable and a solid, thus making it easier to work with. This was one of the first aspects explored when we carried our initial investigations (Table 2-4.1)

Table 2-4.1: Optimization of Redox Amination



entry[a]	Indoline	additive	R	solvent	time (h)	yield (%)
1	**1**	10% $PhCO_2H$	H	Toluene	18h	0
2	**1**[b]	10% $PhCO_2H$	H	Toluene	0.5	trace
3	**2**	10% $PhCO_2H$	H	Toluene	12	87
4	**2**	none	H	Toluene	12	88
5	**2**	none	H	EtOH	4	92
6	**2**	none	Bn	MeCN	15	63
7	**2**	none	Bn	Toluene	16	88
8	**2**	none	Bn	*t*-BuOH	12	73
9	**2**	none	Bn	THF	48	0
10	**2**	none	Bn	1,2 DCE	72	20
11	**2**	none	Bn	H_2O	24	~5[c]
12	**2**	none	Bn	EtOH	4	91
13	**2**[b]	none	Bn	EtOH	0.5	54

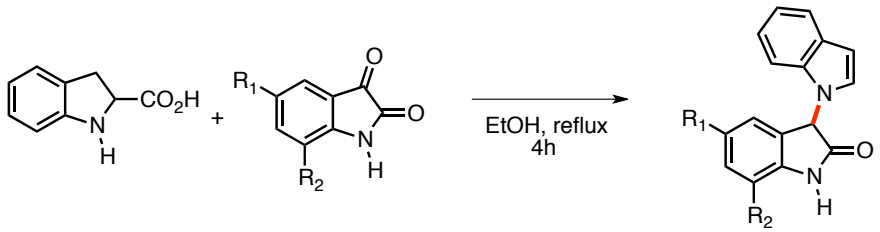
[a] Reaction run 0.5 mmol in 2 mL solvent. [b] Reaction run in microwave at 200°C.
[c] Based on NMR of crude reaction mixture.

The differences in reactivity of indoline and pyrroline were immediately apparent. When isatin and indoline were reacted under the same conditions that pyrroline was shown to furnish product, no reaction was observed (Table 2-4.1, Entry 1). Switching to microwave conditions as shown by Seidel produced trace amounts of product (Entry 2). The key to success in this redox amination came in switching from indoline to indoline-2-carboxylic acid, which generated the desired N substituted indole in 87% yield (Entry 3). Since indoline-2-carboxylic acid contains a carboxylic acid, the benzonic acid catalyst was not necessary for redox amination to occur (Entry 4). Indoline-2-carboxylic acid is poorly soluble in toluene, and switching to ethanol produced a slightly improved yield and greatly improved reaction time (Entry 5). Due to the difference in solubility between

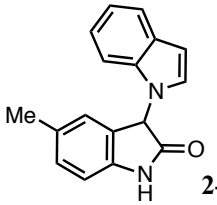
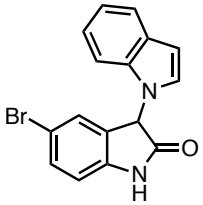
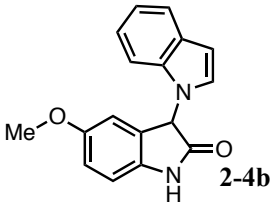
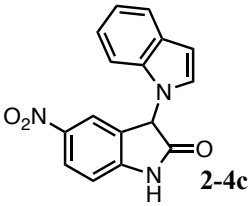
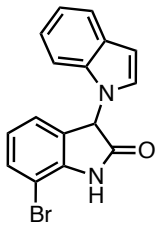
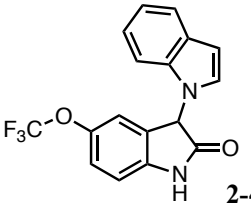
isatins with an N-H bond and isatins containing a substituted nitrogen, conditions were also optimized on N-benzyl isatin as well. While the more soluble benzyl isatin was able to undergo redox amination in a variety of solvents (Entries 6-13), it was found that ethanol was the ideal solvent, indicating that solubility of the indoline 2 carboxylic acid is a key factor in determining the rate of redox amination.

With these optimized conditions, we then set out to explore the scope of redox aminations with isatin. We started by looking at isatins with out substitutions on the nitrogen (Table 2-4.2).

Table 2-4.2: Redox aminations with unsubstituted isatins



2-4(a-g)

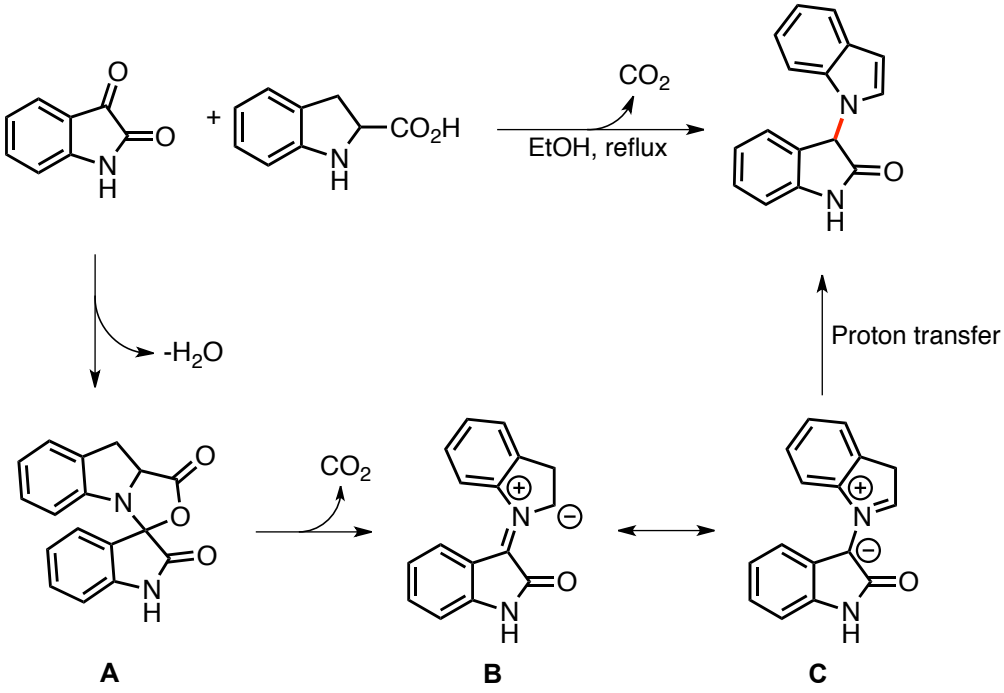
entry	product	yield[a]	entry	product	yield
1	 **2-4a**	92%	5[b]	 **2-4e**	43%
2	 **2-4b**	90%	6	 **2-4f**	84%
3	 **2-4c**	78%	7	 **2-4g**	86%
4	 **2-4d**	70%			

[a] Isolated yield. [b] Reaction required 9h to go to completion.

The redox amination was high yielding with electron donating substituents on the isatin including methyl (Entry 1) and methoxy (Entry 2). There is a distinct decrease in yield when the isatin contains electron withdrawing groups (Entries 3-4). This could be due to the inability of the electron withdrawing group to stabilize an iminium. With

halogenated isatins, there is a drastic difference in reactivity between isatin with a bromine in the 5-position (Entry 5) and fluorine in the 5-position (Entry 6), with the bromoisatin requiring a longer reaction time and providing a lower yield. This difference seems to be a steric issue, perhaps the larger bromine blocks the iminium formation. The fact that 7-bromo isatin (Entry 7) does not have such issues lends credence to this, though it does not explain how a nitro group or a methoxy group do not impede redox amination. With this information combined with data from similar reactions, a cromulent mechanism is proposed (Figure 2-3.1).

Figure 2-4.1: Proposed Mechanism

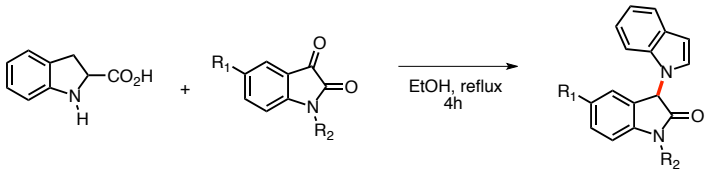


The reaction begins with condensation of the isatin and indoline-2-carboxylic acid to form the 5-member spirocycle **A**. Decarboxylation of this intermediate then produces azomethine ylide **B** which then resonates to intermediate **C**, which then undergoes proton transfer to yield the product indole via redox amination. The five member spricocycle **A**

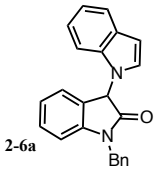
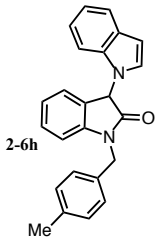
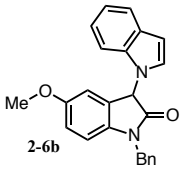
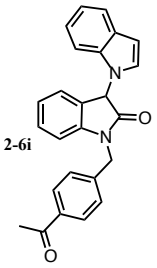
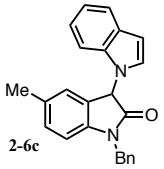
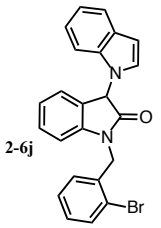
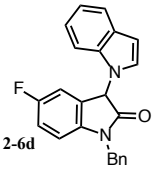
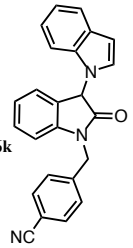
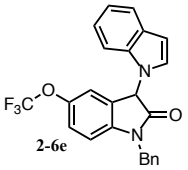
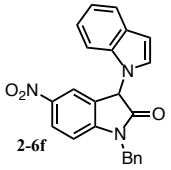
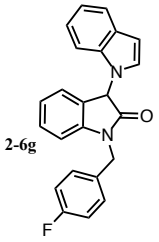
is similar to an intermediate seen by Grigg, and similar secondary α amino acids are known to form azomethine ylide upon condensation.[9] It appears the decarboxylation is necessary in this redox amination, since indoline was found to be non-reactive. Reaction of the ethyl ester of indoline-2-carboxylic acid with isatin did not produce the desired redox amination product. With this information we then explored the range of this redox amination with isatins containing benzyl substitutions at the nitrogen (Table 2-4.3).

Many of the trends for N-benzyl isatins are similar to those for N-H isatins. Benzyl isatins with alkyl, electron donating, or fluoro groups on them undergo redox amination to give high yield (Entries 2-4). There is also the same drop in yield when seen when switching to a highly electron withdrawing group such as trifluoromethoxy (Entry 5) or nitro (Entry 6). We then chose to use the modular nature of the benzyl group to explore functional group compatibility by using substituted benzyl isatins. The fluorinated benzyl group also gave very high yield (Entry 7). A methyl benzyl group (Entry 8) had very similar effect on yield as a benzyl group. Isatin containing an acetophenone (entry 9) was particularly interesting, since it possesses two carbonyls that could under go redox amination but only reaction with the carbonyl on the isatin is observed. A bulky substituent in the ortho position of benzyl group is tolerated (Entry 10). The nitrile benzyl group also reacts cleanly to give the product (Entry 11) indicating that redox amination tolerates electron withdrawing groups on the benzyl moiety and that the nitrile itself does not react under the reaction conditions.

Table 2-3.3 Redox Aminations with N-Benzyl Substituted Isatins

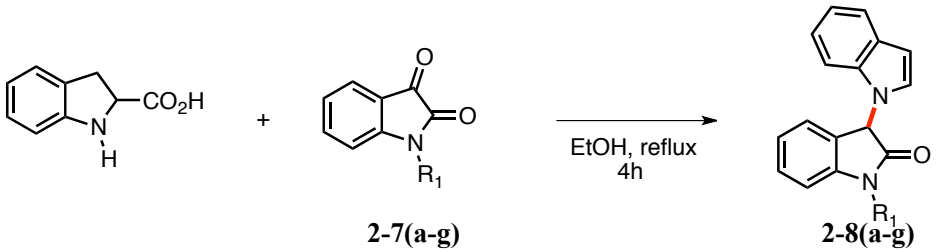


2-5(a-k) **2-6(a-k)**

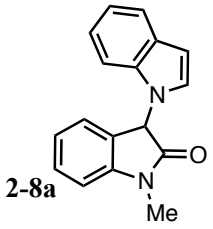
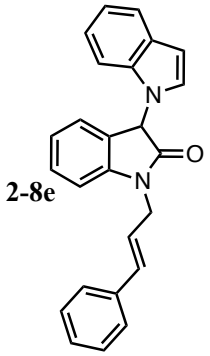
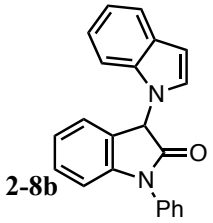
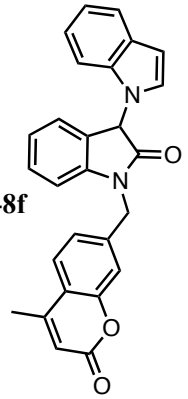
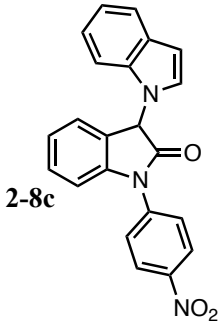
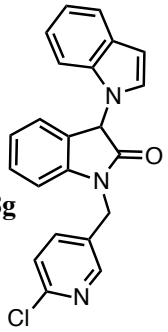
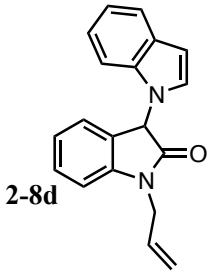
entry	product	yield	entry	product	yield
1	 **2-6a**	91%	8	 **2-6h**	88%
2	 **2-6b**	85%	9	 **2-6i**	66%
3	 **2-6c**	80%	10	 **2-6j**	71%
4	 **2-6d**	91%	11	 **2-6k**	68%
5	 **2-6e**	61%			
6	 **2-6f**	71%			
7	 **2-6g**	95%			

We then chose to extend our redox amination beyond benzyl isatins (Table 2-4.4). Isatins with a variety of variety of hydrocarbon groups attached undergo redox amination, though is a distinct decrease in yield as mass of the alkyl group increases, with methyl isatin (Entry 1) giving the highest yield and a decrease is yield and as it is extended to allyl (Entry 4) and cinnamyl (Entry 5) moieties. Aryl isatins were a unique case. While phenyl isatin (Entry 2) gave the desired product in good yield, 4-nitro phenyl isatin (Entry 3) did not. This was indicative of a trend. It is known that isatins with electron withdrawing groups on the nitrogen will undergo a ring opening reaction (Scheme 2-4.1).[10] Even when the solvent is switched to non-nucleophilic toluene, a low yield was obtained. Similar results were observed with N-acyl isatin and N-boc isatin. Finally, isatins with biologically significant heterocycles were subjected to redox amination conditions. Isatins bearing a coumarin (Entry 6) and pyridine (Entry 7) show that redox amination is a viable way to synthesize N-substituted indoles containing motifs commonly found in biological systems.

Table 2-4.4: Redox Aminations with N-Substituted Isatins

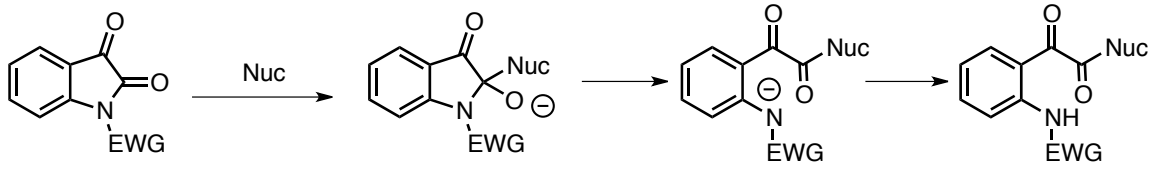


2-7(a-g) **2-8(a-g)**

entry	product	yield	entry	product	yield
1	 **2-8a**	91%	5	 **2-8e**	44%
2	 **2-8b**	84%	6[b]	 **2-8f**	59 %
3[a]	 **2-8c**	39%	7	 **2-8g**	64 %
4	 **2-8d**	63%			

[a] Reaction run in toluene. [b] Reaction run in 0.025 mM for 12 h.

Scheme 2-4.1: Ring Opening of Isatins Containing EWG's



Isatins have been shown to undergo redox amination with indoline-2-carboxylic acid to provide N substituted indoles bearing an indolinone. To our knowledge, this is the first instance of indoline or indoline-2-carboxylic acid undergoing redox amination with a ketone of any kind. This reaction is compatible with a wide variety of isatins. This reaction is also environmentally benign, requiring no catalyst and only producing CO_2 and water as byproducts. Further, isatins scaffolds present in many biological systems are compatible with this methodology.

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[1] Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A.Formation of N-Alkylpyrroles via Intermolecular Redox Amination *J. Am. Chem. Soc.* **2009**, *131*, 16626

[2] DFT calculations hav shown that the proton transfer is not likely intramolecular. Xue, X.; Yu, A.; Cai Y.; Cheng, J. A Computational Reinvestigation of the Formation of *N*-Alkyl Pyrroles via Intermolecular Redox Amination *Org. Lett.* **2011,** *13*, 6054

[3] It was found than when pyrroline was reacted with alpha hydroxy acetophenone, the enamine product was isolable,

[4] Singh, G. S.; Desta, Z. Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks *Chem. Rev.* **2012**, *112*, 6104.

[5] (a) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R.; A Novel One-Pot Synthesis of Some New Interesting Pyrrole Derivatives *J. Org. Chem.* **2005**, *70*, 1471.; (b) Azizian, J.; Karimi, A. R.; Kazemizadeh, Z.; Mohammadi, A. A.; Mohammadizadeh, M. R.;Silica sulfuric acid-catalyzed reaction of 4-hydroxyproline with 11H-indeno[1,2-b]quinoxalin-11-one and isatin derivatives: A novel synthesis of new pyrrole compounds *Synthesis* **2005**, 1095.;(c) Banik, B. K.; Cardona, M.; Bismuth nitrate-catalyzed novel synthesis of pyrrole-substituted indolinones *Tetrahedron Lett.* **2006**, *47*, 7385.; (d) Banik, B. K.; Garcia, I.; Morales, F. R.; Aguilar, C. Novel synthesis of substituted pyrrole bound to indolinone via molecular iodine-catalyzed reaction*Heterocycl. Commun.* **2007**, *13*, 109.; (e) Karimi, A. R.; Mohammadi, A. A. KAl(SO4)2.12H2O supported on silica gel catalyzed coupling of 4-hydroxyproline

with isatins, 11H-indeno[1,2-b]quinoxalin-11-ones, quinones, and 9H-fluoren-9-one. An efficient synthesis of some interesting pyrroles *Lett. Org. Chem.* **2008**, *5*, 566

[6] Tsai, H.-H. G.; Chung, M.-W.; Chou, Y.-K.; Hou, D.-R. Interplay of Hydrogenation and Dehydrogenation in Isoindoline and Indoline Isomers: A Density Functional Theory Study *J. Phys. Chem. A* **2008**, *112*, 5278.

[7] Aly, M. F.; Ardill, H.; Grigg, R.; Leong-Ling, S.; Rajviroongit, S.; Surendrakumar, S.; The reaction of secondary Œ±-amino acids with carbonyl compounds. Properties of the intermediate azomethine ylides. Oxazolidine formation versus 1,4-prototropy *Tetrahedron Lett.* **1987**, *28*, 6077

[8] Deb, I.; Das, D.; Seidel, D.: Redox Isomerization via Azomethine Ylide Intermediates: N-Alkyl Indoles from Indolines and Aldehydes *Org. Lett.* **2011**, *13*, 812

[9] Indoline 2-carboxylic acid and pivaldehyde have been shown by grigg (ref 6) similar to those seen with proline and pivaldehyde Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B.; Alkylation of amino acids without loss of the optical activity: preparation of Œ±-substituted proline derivatives. A case of self-reproduction of chirality *J. Am. Chem. Soc.* **1983**, *105*, 5390.

[10] (a) Jacobs, T. L.; Winstein, S.; Linden, G. B.; Robson, J. H.; Levy, E. F.; Seymour, D.; 2-Hydroxycinchoninic acid *Org. Synth.* **1948**, *28*, 70; (b) Cravotto, G.; Giovenzana, G. B.; Palmisano, G.; Penoni, A.; Pilati, T.; Sisti, M.; Stazi, F.: Convolutamydine A: the first authenticated absolute configuration and enantioselective synthesis*Tetrahedron: Asymmetry* **2006**, *17*, 3070

Chapter 2 Supporting Information

General Information

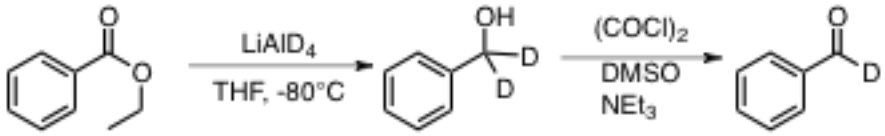
All reactions were run in flame dried glassware under an argon atmosphere. Anhydrous ethanol was used without further purification. Toluene was dried over sodium in the presence of benzophenone indicator. Commercially available reagents were used without additional purification unless otherwise stated. Indoline, indoline 2 carboxylic acid, pyrroline and 2,5 dimethylpyrroline were purchased and used without further purification. Isatins with an unsubstituted N-H as well as **2-5a**, and (**2-7a)-(2-7b)** purchased from commercially available sources and used without further purification. N-substituted isatins were synthesized as described below. TLC analysis was performed with silica gel HL TLC plates w/UV254 from Sorbent Technologies. 60 Å porosity, 230 x 400 mesh standard grade silica gel from Sorbent Technologies was used for flash column chromatography. GC/MS data was obtained using a Shimadzu GCMS-QP2010 SE. ^{1}H and ^{13}C spectra were obtained on a Bruker Advance 500 DRX equipped with a QNP cryoprobe ^{1}H and ^{13}C NMR spectra were referenced to residual protio solvent signals.

Electrospray Ionization spectra were acquired on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. The instrument was operated at 10,000 resolution (W mode) with dynamic range enhancement that attenuates large intensity signals. The cone voltage was 60eV. Spectra were acquired at 16666 Hz pusher frequency covering the mass range 100 to 1200 u and accumulating data for 2 seconds

per cycle. Mass correction for exact mass determinations were made automatically with the lock mass feature in the MassLynx data system. A reference compound in an auxiliary sprayer is sampled every third cycle by toggling a "shutter" between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles. Samples are presented in acetonitrile (or your solvent here) as a 100uL loop injection using an auto injector (LC PAL, CTC Analytics AG, Zwingen, Switzerland)The Gas Chromatography-Mass Spectrometric data were collected on an Agilent 6890N Gas Chromatograph interfaced with quadrupole mass analyzer (Quattro Micro GC, Waters corp., Milford MA). A 5% phenyl, methyl silicone stationary phase (HP-5MS), 15 meter column with a 0.25" ID was used. The carrier gas was helium and constant flow mode was used to maintain 1.5 mL/min. Injections of 1.0 uL were made into the injector port heated to 240°C and a split ratio of 20:1 was used. The GC thermal gradient was an initial 50°C with a 1 minute hold after which the temperature was increased 25 °C/min to a final temperature of 300° C and held for 2 minutes. Ionization was by electron impact at 70eV and the mass analyzer scanned from 45 to 600 u in 0.5 seconds. The analyzers were tuned to 0.6 u FWHH and data collected in centroid mode.

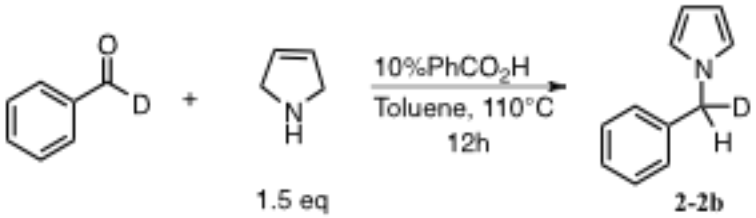
Deuterium Labeling Studies

Deutero Benzaldehyde



Deuterobenzaldehyde was prepared according to the method of Dong and coworkers. All spectra were the same as those previously reported.[1]

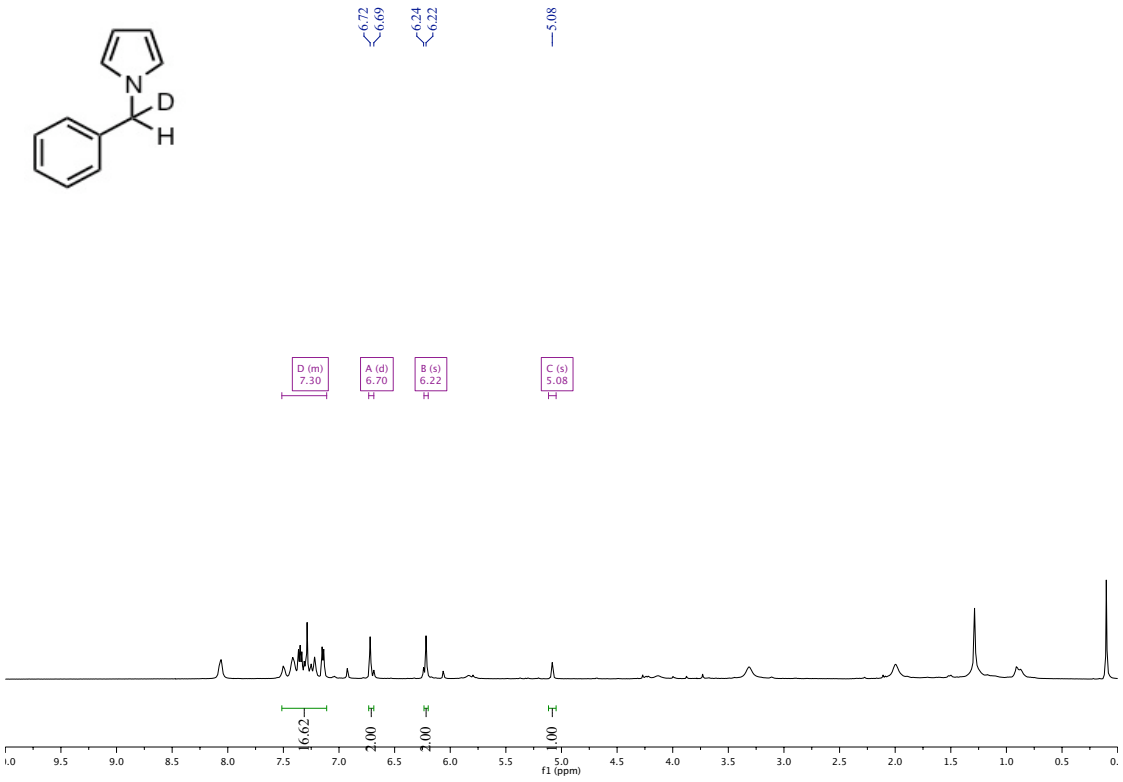
Deuterium Retention



[1] Matthew M. Coulter, Peter K. Dornan, and Vy M. Dong Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality *J. Am. Chem. Soc.* **2009** *131* (20), 6932-6933

1-benzyl-1D-pyrrole

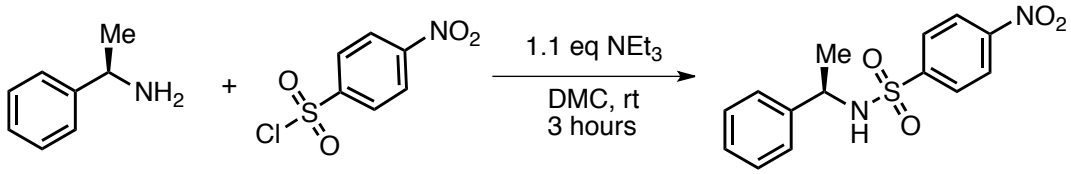
In a dried 5ml sealed tube was added 6.1 mg benzoic acid (0.05 mmol) and 50.7 μL deuterated benzaldehyde (0.5 mmol). The vessel was then sealed. Through the cap, 2 mL of dried toluene was added, followed by 57 μL of pyrrolidine (0.75 mmol). The reaction was heated to 110ºC for 12 hours, after which the reaction was cooled to room temperature. The solvent was removed, and removed via azeotroping with added chloroform (3 mL x 5 times. An NMR was taken of the crude mixture so as to eliminate the possibility of proton exchange through any workup. The crude NMR showed distinct peaks indicative of a pyrrole at 6.70 and 6.02 ppm. Both of these peaks integrated to 2, while the benzyl protons corresponded to 1. In literature spectra for N –benzyl pyrrole, the benzylic protons integrate to 2 and are at found at ~5 ppm. In this case the benzyl protons integrated to 1, indicating the complete retention of deuterium in the reaction.



Attempts at Enantioselectivity

All catalysts were purchased and used without further purification. All chiral molecules were purchased as used without further purification. All thioureas and phosphoric acids were purchased and used without further purification Any sulfonamines were prepared using the general procedure shown below.

General Procedure for sulfonamides



To a dried round bottom flask was added 1.030 mL of R-phenyl ethyl amine (8 mmol), 1.228 mL of NEt_3 (8.8 mmol), and 80 mL of CH_2Cl_2. Then 1.767 g nosyl chloride (8 mmol) was added at once. The reaction was stirred at rt for three hours. Once the reaction was done by TLC (10% ethyl acetate in hexane) the mixture was then warmed to room temperature and quenched with 40 mL water. The mixture was placed into a sepratory funnel, extracted 3 times with 30 mL dichloromethane. The extractions were combined, washed with brine, and then dried with magnesium sulfate. Drying agent was then filtered off and the solvent was removed by rotory evaporator. The crude product was then recrystallized from acetonitrile.

General procedure for redox amination with pyrroline

The procedure for the synthesis redox amination was the same as that previously published for this reaction.[2].

Determination of ee

[2] Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. Formation of N-Alkylpyrroles via Intermolecular Redox Amination *J. Am. Chem. Soc.* **2009**, *131*, 16626.

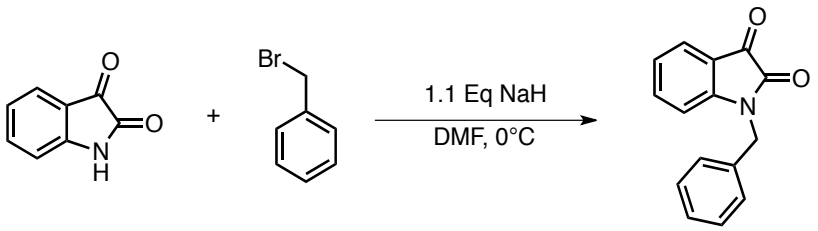
All products of synthesis using a chiral catalyst were purified via column chromatography then analyzed using a chiral HPLC. The column used was a chiralpack OD-H column, run at 99% hexanes/1% isopropanol at a rate of 0.5 mL/minute. Elution times for the racemic mixtures were 35 and 37 minutes. All compounds tested this way were found to be racemic.

Synthesis of N substituted Isatins

All isatins with a free N-H were purchased and used without further purification. N-substituted isatins were either purchased or synthesized via benzylation procedure A. Spectra and masses for isatins **2-5(A-F), 2-5j, 2-7a** and **2-7b** were identical to those reported in literature.[3,4,5]

[3] Vyas, D.J.; Fröhlich, R.; and Oestreich, M. Stereochemical Surprises in the Lewis Acid-Mediated Allylation of Isatins *J. Org. Chem.* **2010** *75* (19), 6720-6723
[4]Singh, R. P.; Majumder, U.; and, and Shreeve, J. M. Nucleophilic Di- and Tetrafluorination of Dicarbonyl Compounds *J. Org. Chem* **2001** *66* (19), 6263-6267
[5] Aikawa, K.; Mimura, S.; Numata, Y.; and Mikami, K. Palladium-Catalyzed Enantioselective Ene and Aldol Reactions with Isatins, Keto Esters, and Diketones: Reliable Approach to Chiral Tertiary Alcohols *Eur. J. Org. Chem*. **2011**, 62–65

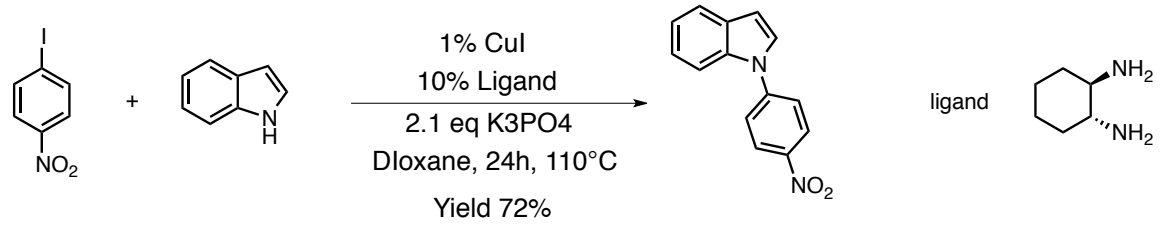
General Procedure for Benzylation of Isatins



Isatin, (294 mg, 2 mmol) was added to 20 mL of DMF and the reaction was cooled to 0 ºC. then, NaH (52 mg, 2.2 mmol) was added slowly. Upon formation of a purple solution and the cessation of bubbles, the reaction was stirred for 5 minutes at 0ºC. To this was then added the benzyl bromide (261 uL, 2.0 mmol) and the reaction was warmed to room temperature. After 2h, the reaction was complete by TLC analysis. It was quenched with 15 mL saturated ammonium chloride, extracted with 3x 20 mL of ethyl acetate. The combined organic phases were then washed with brine and dried with magnesium sulfate. The solvent was removed by rotary evaoporation and the residue was purified via column chromatography (30% ethyl acetate/hexanes) to give the pure isatin. Alternately, the product could also be purified by recrystalization from ethanol. Isatins **2-5(a-g)**, **2-5j**, **2-7(a-b)**, and **2-7d** were identical to literature values previously reported.

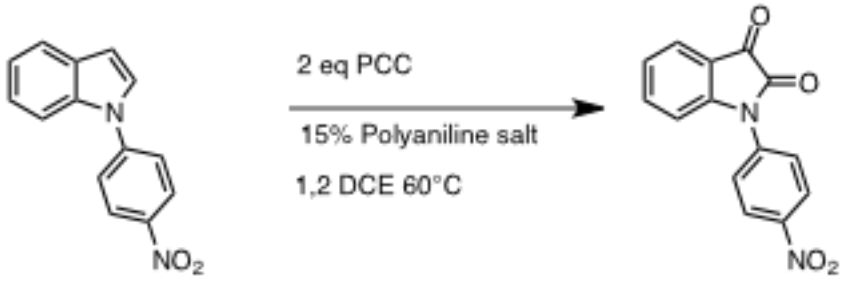
1-(4-nitrophenyl)isatin (17c)

i) synthesis of 1-(4-nitrophenyl)-indole



1-(4-nitrophenyl)-1H-indole was synthesized via literature procedure from indole and 4-iodonitrobenzene.[6]

ii) 1-(4-nitrophenyl)isatin



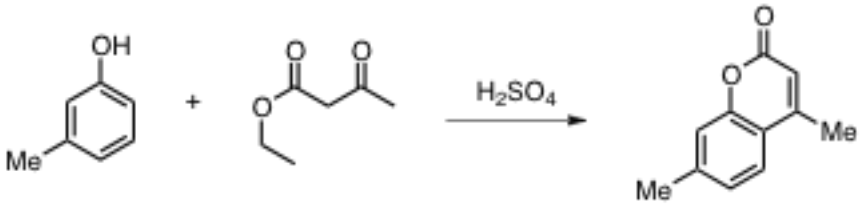
1-(4-nitrophenyl)isatin was prepared following a modified literature procedure.[7] 1-(4-nitrophenyl)indole (476.1 mg, 2 mmol) was added to a Schlenk flask, along with a stir

[6] Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. A general and efficient copper catalyst for the amidation of aryl halides and the N-arylation of nitrogen heterocycles *J. Am. Chem. Soc.* **2001**, *123*, 7727.

bar and pyridinium chlorochromate (862.24 mg, 4 mmol) and polyaniline salt (25 mg). The flask was filled with argon, filled with dichloroethane (25ml) and heated to 60ºC for 12h. When reaction was finished by TLC, the reaction was cooled to room temperature and quenched with water. The mixture was extracted 3 times with dichloromenthane, brined, and dried with magnesium sulfate. The reaction mixture was the filtered and the product was purified by column chromatography (5%-40% ethyl acetate/hexanes) to give the product as a bright yellow solid.

4-methyl-7-bromomethyl-coumarin

i) Synthesis of 4,7-dimethylcoumarin



m-cresol (10.45 mL, 100 mmol) and ethylacetoacetate (12.647 mL, 100 mmol) were added to 15 mL of sulfuric acid. The reaction was allowed to stir at room temperature for 24 hours. The reaction was quenched by adding 20 g of ice, at which time a white precipitate formed. When the ice had melted, the precipitate was filtered off, and the precipitate was recrystallized from EtOH to give the desired coumarin as a white solid (2.298g, 13.2 %) **^{1}H NMR (500 MHz, $CDCl_3$)** 7.36 (d, *J* = 8.0 Hz, 1H), 6.95 (m, 2H), 6.09 (d, *J* = 1.1 Hz, 1H), 2.32 (s, 3H), 2.30 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) 161.16, 153.46, 152.62, 142.92, 125.39, 124.30, 117.49, 117.06, 113.82, 21.56, 18.58.

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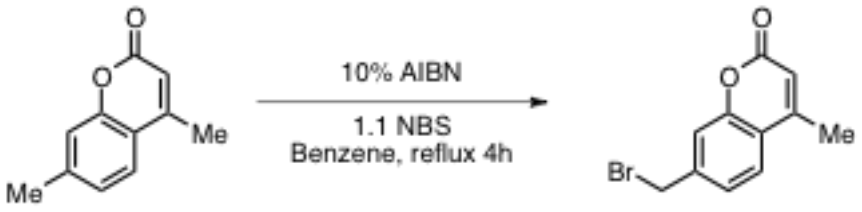
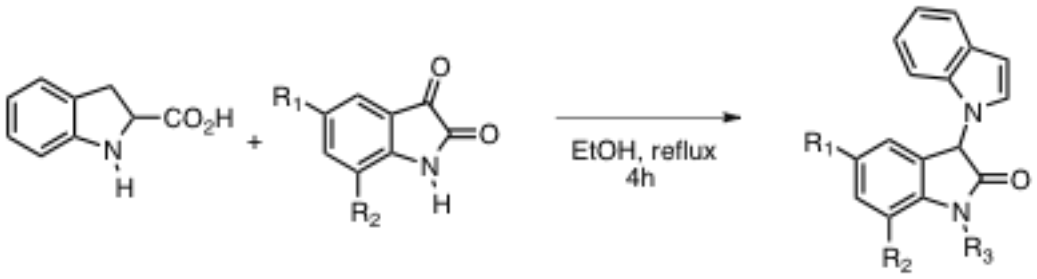
[7] Kumar, C. N. S. S. P.; Devi, C. L.; Rao, V. J.; Palaniappan, S. Use of pyridinium chlorochromate and reusable polyaniline salt catalyst combination for the oxidation of indoles *Synlett* **2008**, 2023.

ii) Synthesis of 4-methyl-7-bromomethyl-coumarin



dimethyl coumarin (1.74g, 10 mmol), AIBN (164 mg, 1mmol) and NBS (1.95g, 11 mmol) were combined in a 100 mL round bottom flask, and 50 ml of benzene was added. A reflux condenser was attached and the reaction was heated at reflux for 4 hours. After that time, the reaction was cooled to room temperature, then to 0ºC. The precipitate was filtered off, and then recrystalized from EtOH to give the desired bromocoumarin (2.23g, 89%) as a white solid. **4-methyl-7-bromomethyl-coumarin ^{1}H NMR (500 MHz, $CDCl_3$)** 7.52 (d, *J* = 8.0 Hz, 1H), 7.22 (m, 2H), 6.23 (d, *J* = 1.1 Hz, 1H), 4.45 (s, 2H), 2.37 (d, *J* = 1.1 Hz, 3H**).** ^{13}**C NMR (126 MHz, $CDCl_3$)** 160.49, 153.49, 151.86, 141.87, 125.12, 124.94, 119.89, 117.37, 115.49, 31.77, 18.68.**HRMS (** Calculated ($C_{11}H_9BrO_2$+H) 252.9864 Found 252.9879

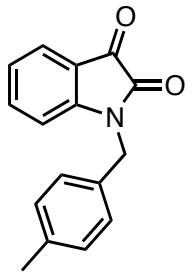
General Procedure for Redox Amination of Isatin and Indoline-2-carboxylic acid



To a flame dried 10 mL round bottom flask was added indoline-2-carboxylic acid (81.5 mg, 0.5 mmol) and the corresponding isatin (0.5mmol). The flask was filled with 2 mL ethanol, attached to a reflux condenser, and heated to reflux. After 4 hours, the reaction was checked via TLC. Upon completion of the reaction, the reaction mixture was rotovapped down, taken up in dichloromethane and dried with magnesium sulfate. The mag sulfate was then filtered off and the reaction mixture was purified via column chromatography to give the product 1,3-bisindole.

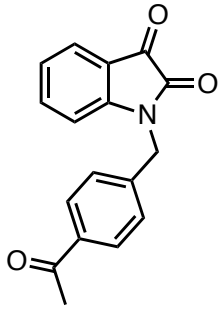
Spectral Data for New Isatins

2-6h) 1-(4-methylbenzyl)indoline-2,3-dione



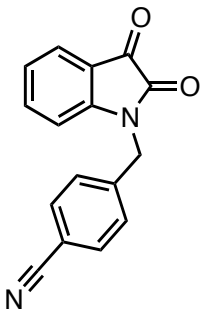
^{1}H NMR (500 MHz, $CDCl_3$) 7.54 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.39 (m, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.01 (td, *J* = 7.6, 0.7 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 4.82 (s, 2H), 2.26 (s, 3H**). ^{13}C NMR (126 MHz, $CDCl_3$)** 183.37, 158.26, 150.80, 138.28, 138.01, 131.43, 129.72, 127.47, 125.41, 123.81, 117.69, 111.04, 43.84, 21.14. **HRMS** Calculated 252.1025 ($C_{16}H_{13}NO_2$+H) Found 252.1018

2-6i) 1-(4-acetylbenzyl)indoline-2,3-dione



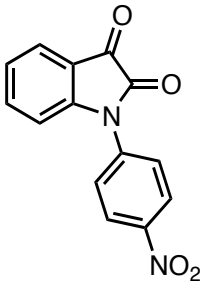
^{1}H NMR (500 MHz, $CDCl_3$) 7.97 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.10 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 2H), 2.61 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 197.42, 182.86, 158.26, 150.34, 139.72, 138.41, 136.98, 129.13, 127.52, 125.66, 124.17, 117.72, 110.78, 43.75, 26.67. **HRMS** Calculated ($C_{17}H_{13}NO_3$+H) 280.0974 Found 280.0995

2-6k) 4-((2,3-dioxoindolin-1-yl)methyl)benzonitrile



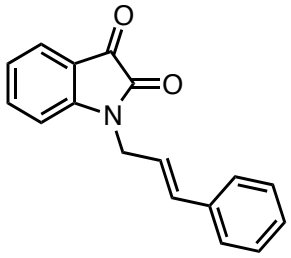
^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.40 (m, 1H), 7.25 (ddd, *J* = 9.2, 4.6, 1.5 Hz, 2H), 7.04 (td, *J* = 7.6, 0.7 Hz, 1H), 6.93 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.83 (s, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** 183.08, 163.49, 161.53, 158.23, 150.49, 138.34, 130.30, 129.30, 129.23, 125.58, 124.02, 117.71, 116.15, 115.98, 110.81, 43.39, 25.29. **HRMS** Calculated ($C_{16}H_{10}N_2O_2$+H) 263.0821 Found 263.0836

2-7c) 1-(4-nitrophenyl)indoline-2,3-dione



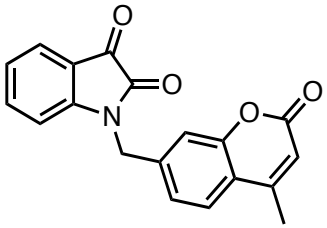
^{1}H NMR (500 MHz, $CDCl_3$) 8.34 (m, 2H), 7.71 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.61 (m, 2H), 7.56 (td, *J* = 7.9, 1.3 Hz, 1H), 7.21 (dd, *J* = 7.5, 0.5 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 180.42, 155.79, 148.99, 145.90, 137.55, 127.31, 125.24, 125.04, 124.31, 124.20, 116.74, 110.19. **HRMS** Calculated ($C_{14}H_8N_2O_4$-H) 267.0406 Found 267.0409

2-7e) 1-cinnamylindoline-2,3-dione ^{1}H NMR



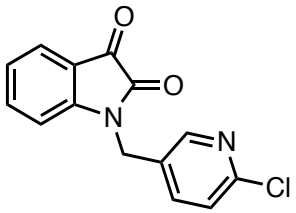
(500 MHz, $CDCl_3$) 7.53 (m, 1H), 7.49 (td, *J* = 7.8, 1.3 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.21 (m, 2H), 7.19 (d, *J* = 3.3 Hz, 1H), 7.05 (td, *J* = 7.6, 0.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.47 (dd, *J* = 6.1, 1.5 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** 183.31, 157.95, 150.83, 138.40, 135.75, 134.08, 128.71, 128.28, 126.52, 125.49, 123.87, 121.49, 117.67, 110.89, 42.21. **HRMS** Calculated ($C_{17}H_{13}NO_2$+H) 264.1025 Found 264.1041

2-7f) 1-((4-methyl-2-oxo-2H-chromen-7-yl)methyl)indoline-2,3-dione



^{1}H NMR (500 MHz, $CDCl_3$) 7.59 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 (td, *J* = 7.8, 1.3 Hz, 1H), 7.20 (m, 2H), 7.07 (td, *J* = 7.6, 0.7 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 4.95 (s, 2H), 2.35 (d, *J* = 1.3 Hz, 3H)**.^{13}C NMR (126 MHz, $CDCl_3$)** 182.69, 160.32, 158.21, 153.77, 151.91, 150.18, 138.90, 138.47, 125.76, 125.58, 124.28, 123.05, 119.81, 117.72, 115.84, 115.39, 110.68, 43.49, 18.66. **HRMS** Calculated (2($C_{19}H_{13}NO_4$)+H) 639.1767 Found 639.178

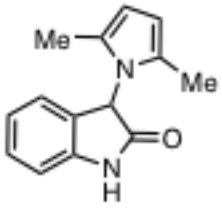
2-7g) 1-((6-chloropyridin-3-yl)methyl)indoline-2,3-dione



1H NMR (500 MHz, CDCl3) δ 8.45 (d, J = 2.5 Hz, 1H), 7.66 (ddd, J = 7.5, 3.9, 1.9 Hz, 2H), 7.55 (td, J = 7.8, 1.4 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.15 (td, J = 7.5, 0.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 4.93 (s, 2H). **13C NMR (125 MHz, CDCl3)** δ 182.45, 158.23, 151.68, 149.76, 148.83, 138.51, 138.24, 129.46, 125.88, 124.91, 124.41, 117.73, 110.36, 40.87 **HRMS** Calculated:($C_{14}H_9ClN_2O_2$+H) 273.0431; found 273.0431

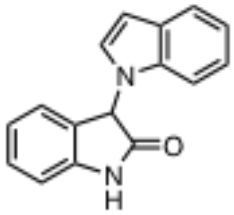
Spectral Data for Indolin-2-ones

2-1b) 3-(2,5-dimethyl-1H-pyrrol-1-yl)indolin-2-one



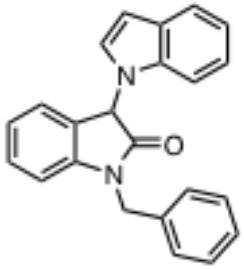
^{1}H NMR (400 MHz, $CDCl_3$) 9.01 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.09 (dt, *J* = 14.9, 7.4 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.91 (d, *J* = 3.2 Hz, 1H), 5.82 (d, *J* = 3.0 Hz, 1H), 5.67 (s, 1H), 2.44 (s, 3H), 1.73 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 175.3, 139.5, 128.5, 128.3, 127.0, 125.2, 123.3, 122.2, 109.8, 106.3, 105.3, 56.3, 11.9,11.3. **HRMS** Calculated ($C_{14}H_{14}N_2O$+H) 227.1184 found 227.1200

2-2a) 3-(1H-indol-1-yl)indolin-2-one



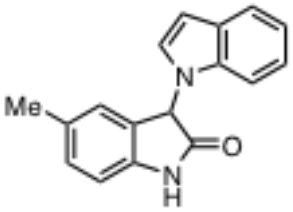
^{1}H NMR (500 MHz, $CDCl_3$) 8.79 (s, 1H), 7.53 (m, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.01 (m, 4H), 6.91 (m, 2H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 5.82 (s, 1H)**. ^{13}C NMR** (126 MHz, $CDCl_3$) 174.0, 139.9, 135.1, 129.1, 128.2, 126.1, 124.2, 124.0, 122.3, 121.2, 120.2, 119.1, 109.7, 108.6, 102.1, 57.9. **HRMS** Calculated ($C_{16}H_{12}N_2O$ + H) 249.0928 found 249.1030

2-2b) 1-benzyl-3-(1H-indol-1-yl)indolin-2-one



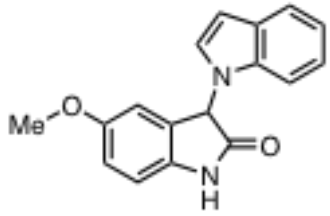
^{1}H NMR (500 MHz, $CDCl_3$) 7.72 (m, 1H), 7.34 (m, 6H), 7.19 (m, 3H), 7.15 (d, *J* = 3.0 Hz, 2H), 7.07 (td, *J* = 7.6, 0.8 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.70 (dd, *J* = 3.2, 0.7 Hz, 1H), 6.01 (s, 1H), 5.13 (d, *J* = 15.5 Hz, 1H), 4.98 (d, *J* = 15.4 Hz, 1H).**^{13}C NMR** (126 MHz, $CDCl_3$)172.8, 143.1, 135.6, 130.2, 129.4, 129.1, 128.1, 127.9, 125.2, 124.7, 123.5, 122.2, 121.4, 120.3, 110.0, 103.2, 58.7, 44.3.**HRMS** Calculated($C_{23}H_{18}N_2O$+ H) 339.1497 found 339.1492

2-a) 3-(1*H*-indol-1-yl)-5-methylindolin-2-one



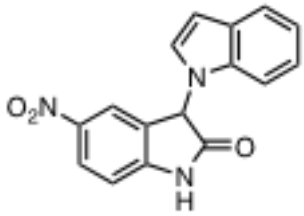
^{1}H NMR (500 MHz, $CDCl_3$) 9.39 (s, 1H), 7.55 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.98 (m, 3H), 6.88 (m, 2H), 6.80 (s, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 5.71 (s, 1H), 2.10 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) 175.7, 138.6, 136.2, 133.0, 130.5, 129.2, 125.7, 125.2, 122.3, 121.3, 120.2, 110.8, 109.8, 103.1, 77.3, 59.2, 21.1**HRMS** Calculated ($C_{17}H_{14}N_2O$+H) 263.1184 found 263.1139.

2-4b) 3-(1H-indol-1-yl)-5-methoxyindolin-2-one



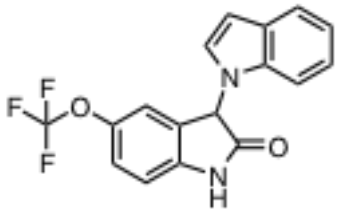
^{1}H NMR (500 MHz, $CDCl_3$) ? 9.39 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.03 (d, *J* = 5.7 Hz, 3H), 6.94 (s, 1H), 6.57 (m, 2H), 6.46 (m, 2H), 5.70 (s, 1H), 3.53 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) 174.4, 155.2, 135.1, 133.3, 128.1, 126.2, 125.2, 121.2, 120.2, 119.1, 114.1, 110.6, 110.4, 108.7, 102.1, 58.4, 54.7. **HRMS** Calculated ($C_{17}H_{14}N_2O_2$-H) 277.0977 found 277.0806

2-4c) 3-(1H-indol-1-yl)-5-nitroindolin-2-one



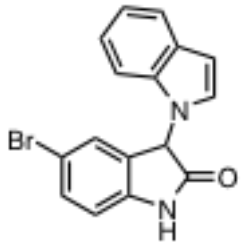
^{1}H NMR (500 MHz, $CDCl_3$) 9.38 (s, 1H), 7.94 (ddd, *J* = 8.7, 2.2, 0.6 Hz, 1H), 7.82 (s, 1H), 7.54 ? 7.49 (m, 1H), 7.03 (dd, *J* = 5.8, 2.8 Hz, 2H), 6.90 (s, 2H), 6.49 (dd, *J* = 3.2, 0.5 Hz, 1H), 6.43 (d, *J* = 8.7 Hz, 1H), 5.72 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) 174.5, 145.4, 142.8, 134.7, 130.0, 128.2, 127.8, 125.9, 124.6, 121.6, 120.6, 119.8, 119.7, 109.9, 108.2, 102.9, 57.5. **HRMS** Calculated ($C_{16}H_{11}N_3O_3$-H) 292.0722 found 292.0466

2-4d) 3-(1H-indol-1-yl)-5-(trifluoromethoxy)indolin-2-one



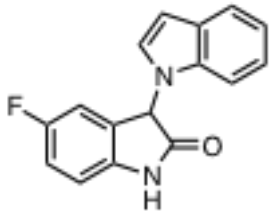
^{1}H NMR (500 MHz, $CDCl_3$) 9.47 (s, 1H), 7.68 (dd, *J* = 6.1, 2.6 Hz, 1H), 7.18 (dd, *J* = 9.5, 4.9 Hz, 2H), 7.05 (m, 2H), 7.02 (s, 2H), 6.62 (dd, *J* = 10.5, 5.9 Hz, 2H), 5.85 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) 175.5, 145.1, 139.7, 136.2, 129.3, 127.0, 126.4, 123.3, 122.5, 121.5, 120.5, 119.4, 118.9, 111.8, 109.5, 103.7, 59.0. **HRMS** Calculated ($C_{17}H_{11}F_3N_2O_2$-H) 331.0700 Found 331.0703

2-4e) 5-bromo-3-(1H-indol-1-yl)indolin-2-one



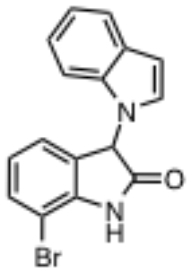
^{1}H NMR (500 MHz, $CDCl_3$) 9.36 (s, 1H), 7.54 (m, 1H), 7.19 (ddd, *J* = 8.4, 1.9, 0.8 Hz, 1H), 7.10 (s, 1H), 7.04 (m, 2H), 6.93 (m, 1H), 6.91 (s, 1H), 6.50 (dd, *J* = 3.2, 0.6 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 5.71 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) 175.1, 134.0, 136.0, 133.1, 129.2, 128.1, 127.1, 127.0, 122.5, 121.5, 120.5, 116.0, 112.6, 109.5, 103.6, 58.9. **HRMS** Calculated ($C_{16}H_{11}BrN_2O$-H) 324.9976 Found 324.9857

2-4f) 5-fluoro-3-(1H-indol-1-yl)indolin-2-one



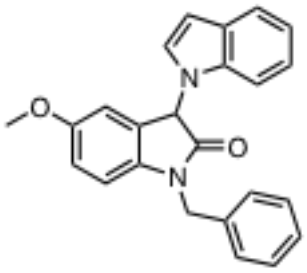
^{1}H NMR (500 MHz, $CDCl_3$) 9.16 (s, 1H), 7.57 (ddd, *J* = 6.9, 4.2, 2.5 Hz, 1H), 7.04 (m, 2H), 6.89 (m, 2H), 6.83 (m, 1H), 6.77 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.60 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.52 (dd, *J* = 3.2, 0.5 Hz, 1H), 5.77 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) 175.3, 160.3, 158.4, 136.86, 136.84, 129.3, 126.53, 126.5, 122.5, 121.4, 120.4, 116.9, 116.7, 113.2, 113.0, 111.8, 111.7, 109.6, 103.5, 59.3. **HRMS** ($C_{16}H_{11}FN_2O$+H) Calculated 267.0934 Found 267.0923

2-4g) 7-bromo-3-(1H-indol-1-yl)indolin-2-one

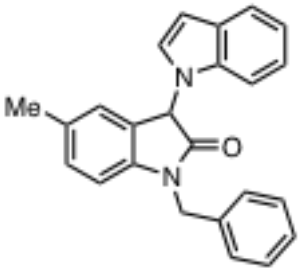


^{1}H NMR (500 MHz, $CDCl_3$) 8.26 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.06 (ddd, *J* = 15.7, 10.8, 4.0 Hz, 3H), 6.91 (m, 2H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 3.0 Hz, 1H), 5.89 (s, 1H)**. ^{13}C NMR** (126 MHz, $CDCl_3$) 173.29, 140.80, 140.25, 136.12, 132.83, 129.19, 127.00, 126.50, 124.97, 124.60, 124.37, 124.08, 122.42, 121.36, 120.36, 109.54, 103.52, 59.74. **HRMS** Calculated **(**$C_{16}H_{11}BrN_2O$-H) 324.9976 Found 324.9681

2-6b) 1-benzyl-3-(1H-indol-1-yl)-5-methoxyindolin-2-one

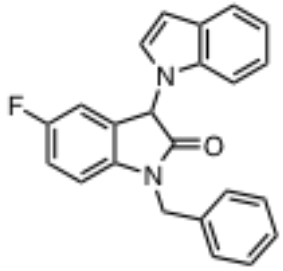


^{1}H NMR (500 MHz, $CDCl_3$) 7.53 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.17 (m, 5H), 6.98 (ddd, *J* = 26.6, 14.7, 4.0 Hz, 4H), 6.67 (tdd, *J* = 4.1, 2.7, 1.2 Hz, 3H), 6.44 (m, 1H), 5.78 (s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.4 Hz, 1H), 3.50 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.43, 156.51, 136.28, 135.56, 129.33, 128.96, 128.01, 127.78, 125.90, 122.21, 121.30, 120.21, 114.88, 111.95, 110.45, 109.97, 103.20, 59.00, 55.78, 44.38. **HRMS** Calculated ($C_{24}H_{20}N_2O_2$+H) 368.1603 Found 368.1834



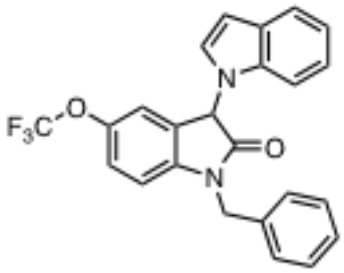
2-6c) 1-benzyl-3-(1H-indol-1-yl)-5-methylindolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) 7.51 (m, 1H), 7.19 (m, 5H), 6.89 (m, 5H), 6.88 (d, *J* = 0.5 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.81 (s, 1H), 4.94 (d, *J* = 15.4 Hz, 1H), 4.79 (d, *J* = 15.4 Hz, 1H), 2.10 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.65, 140.56, 136.21, 135.56, 133.13, 130.34, 129.29, 128.93, 127.98, 127.77, 125.85, 124.74, 122.14, 121.27, 120.14, 109.95, 109.61, 103.08, 58.75, 44.33, 20.99. **HRMS** Calculated ($C_{24}H_{20}N_2O$-H) 351.1503 Found 351.1450

2-6d) 1-benzyl-5-fluoro-3-(1H-indol-1-yl)indolin-2-one



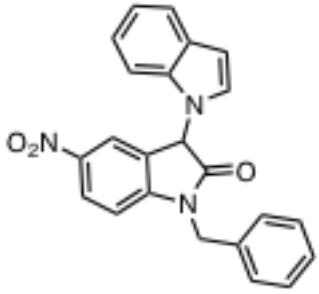
^{1}H NMR (500 MHz, $CDCl_3$) 7.54 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.19 (m, 5H), 6.82 (m, 5H), 6.77 (ddd, *J* = 7.4, 2.5, 1.0 Hz, 1H), 6.67 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.79 (s, 1H), 4.92 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)**172.45, 160.44, 158.50, 138.87, 138.86, 136.08, 135.16, 129.37, 129.17, 129.06, 128.33, 128.18, 127.76, 127.48, 127.26, 126.30, 126.23, 122.34, 121.44, 120.37, 116.64, 116.45, 113.36, 113.16, 110.63, 110.56, 109.76, 103.50, 58.77, 44.47. **HRMS** Calculated ($C_{23}H_{17}FN_2O$) 356.1325 Found 356.1390

2-6e) 1-benzyl-3-(1H-indol-1-yl)-5-(trifluoromethoxy)indolin-2-one



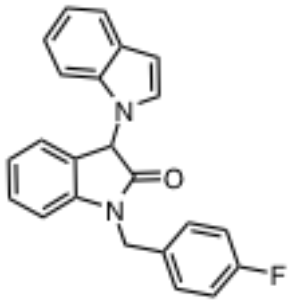
^{1}H NMR (500 MHz, $CDCl_3$) 7.58 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.30 (d, *J* = 1.1 Hz, 2H), 7.24 (m, 2H), 7.19 (s, 2H), 7.04 (m, 3H), 7.00 (s, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.55 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.90 (s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.86 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.43, 145.18, 141.58, 136.10, 134.85, 134.04, 130.95, 129.29, 129.08, 128.45, 128.25, 127.70, 127.45, 126.91, 126.09, 123.26, 122.39, 121.43, 120.39, 119.35, 119.13, 118.54, 112.10, 110.39, 109.55, 103.69, 97.62, 58.46, 44.51, 44.28. **HRMS** Calculated ($C_{24}H_{17}F_3N_2O_2$-H) 421.1164 Found 421.1643

2-6f) 1-benzyl-3-(1H-indol-1-yl)-5-nitroindolin-2-one ^{1}H NMR



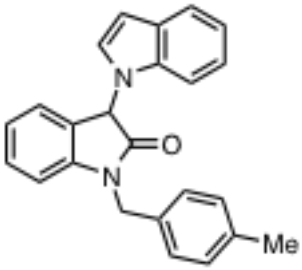
NMR (500 MHz, $CDCl_3$) 8.01 (d, *J* = 8.7 Hz, 1H), 7.82 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.19 (dd, *J* = 13.3, 5.6 Hz, 5H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.92 (dd, *J* = 15.0, 7.0 Hz, 2H), 6.76 (t, *J* = 19.0 Hz, 2H), 6.46 (d, *J* = 3.2 Hz, 1H), 5.80 (s, 1H), 4.93 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 15.5 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.86, 148.36, 143.84, 135.84, 134.40, 133.45, 129.39, 129.30, 129.24, 128.63, 128.56, 127.82, 127.57, 127.36, 127.33, 127.08, 125.56, 122.55, 121.61, 120.84, 120.75, 120.61, 111.25, 109.65, 109.49, 103.90, 58.12, 44.69. **HRMS** Calculated ($C_{23}H_{17}N_3O_3$-H) 382.1197 Found 382.1018

2-6g) 1-(4-fluorobenzyl)-3-(1H-indol-1-yl)indolin-2-one



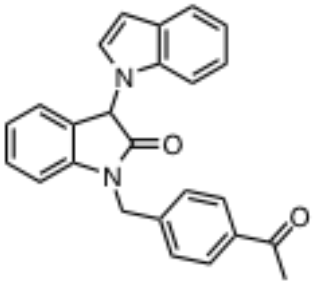
^{1}H NMR (500 MHz, $CDCl_3$) 7.53 (m, 1H), 7.24 (m, 2H), 7.19 (m, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.98 (m, 2H), 6.84 (m, 5H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.50 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.84 (s, 1H), 4.93 (d, *J* = 15.4 Hz, 1H), 4.77 (d, *J* = 15.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.70, 163.43, 161.47, 142.81, 136.16, 131.26, 131.24, 130.12, 129.61, 129.54, 129.32, 127.17, 125.31, 124.64, 123.52, 122.15, 121.32, 120.21, 115.98, 115.81, 109.82, 109.64, 103.21, 58.61, 43.59. **HRMS** Calculated ($C_{23}H_{17}FN_2$-H) 355.1252 Found 355.1263

2-6h) 3-(1H-indol-1-yl)-1-(4-methylbenzyl)indolin-2-one



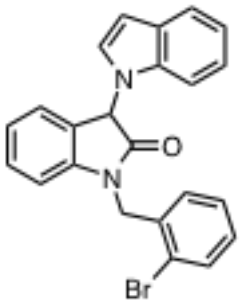
^{1}H NMR (500 MHz, $CDCl_3$) 7.48 (m, 1H), 7.12 (m, 3H), 7.00 (ddd, *J* = 13.3, 11.1, 7.4 Hz, 5H), 6.82 (m, 3H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.47 (dd, *J* = 3.2, 0.6 Hz, 1H), 5.79 (s, 1H), 4.89 (d, *J* = 15.3 Hz, 1H), 4.73 (d, *J* = 15.3 Hz, 1H), 2.22 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.71, 143.09, 137.78, 136.26, 132.45, 130.10, 129.77, 129.65, 129.34, 127.81, 127.56, 127.27, 125.15, 124.72, 123.35, 122.17, 121.30, 120.19, 109.97, 109.92, 103.15, 58.66, 44.09, 21.25 **HRMS** Calculated ($C_{24}H_{20}N_2O$-H) 351.1503 Found 351.1484

2-6i) 1-(4-acetylbenzyl)-3-(1H-indol-1-yl)indolin-2-one ^{1}H



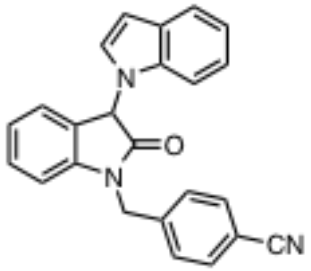
^{1}H NMR (500 MHz, $CDCl_3$) 7.83 (m, 2H), 7.55 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.20 (dd, *J* = 11.3, 4.3 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 7.00 (m, 2H), 6.88 (m, 3H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.50 (dd, *J* = 3.2, 0.6 Hz, 1H), 5.89 (s, 1H), 4.99 (d, *J* = 15.8 Hz, 1H), 4.86 (d, *J* = 15.8 Hz, 1H), 2.49 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 196.50, 171.71, 141.60, 139.60, 135.73, 135.12, 129.10, 128.23, 128.04, 127.94, 126.72, 126.45, 126.02, 124.30, 123.50, 122.58, 121.11, 120.27, 119.17, 108.71, 108.55, 102.20, 57.46, 42.88, 25.62. **HRMS** Calculated ($C_{25}H_{20}N_2O_2$-H) 379.1447 Found 379.1192

2-6j 1-(2-bromobenzyl)-3-(1H-indol-1-yl)indolin-2-one



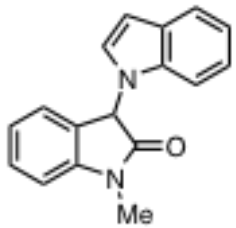
2-6j 1-(2-bromobenzyl)-3-(1H-indol-1-yl)indolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (m, 1H), 7.53 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.01 (m, 7H), 6.93 (m, 2H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.51 (d, *J* = 3.2 Hz, 1H), 5.92 (s, 1H), 4.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$)171.80, 141.71, 135.21, 133.07, 132.06, 129.22, 128.35, 128.22, 127.17, 126.89, 125.96, 124.17, 123.41, 122.54, 121.92, 121.12, 120.25, 119.15, 108.88, 108.77, 102.21, 57.51, 43.07. **HRMS** Calculated ($C_{23}H_{17}BrN_2O$+H) 417.0603 Found 417.0565

2-6k) 4-((3-(1H-indol-1-yl)-2-oxoindolin-1-yl)methyl)benzonitrile



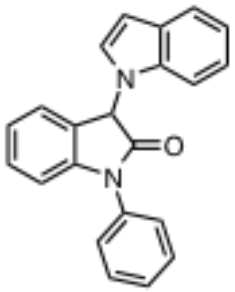
^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (ddd, *J* = 8.4, 4.2, 1.2 Hz, 3H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.21 (m, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.87 (m, 5H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.51 (dd, *J* = 3.2, 0.7 Hz, 1H), 5.89 (s, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H**). ^{13}C NMR (126 MHz, $CDCl_3$)** 171.74, 141.38, 139.72, 135.10, 131.72, 129.20, 128.27, 127.24, 126.00, 124.49, 123.45, 122.78, 121.14, 120.34, 119.24, 117.38, 111.00, 108.64, 108.32, 102.30, 57.44, 42.78. **HRMS** Calculated ($C_{24}H_{17}N_3O$-H) 362.1299 Found 362.1404

2-8a) 3-(1H-indol-1-yl)-1-methylindolin-2-one



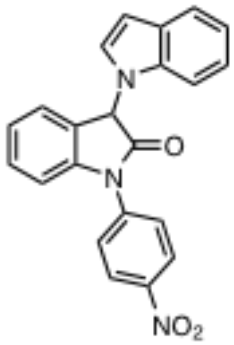
^{1}H NMR (500 MHz, $CDCl_3$) 7.50 (m, 1H), 7.26 (m, 1H), 6.96 (m, 4H), 6.91 (m, 1H), 6.89 (d, *J* = 3.2 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.46 (dd, *J* = 3.3, 0.6 Hz, 1H), 5.74 (s, 1H), 3.18 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.56, 143.92, 136.31, 130.22, 129.23, 127.04, 125.04, 124.71, 123.38, 122.19, 121.27, 120.13, 109.72, 108.84, 103.09, 58.45, 26.66. **HRMS** Calculated ($C_{17}H_{14}N_2O$-H) 261.1028 Found 261.0929

2-8b) 3-(1H-indol-1-yl)-1-phenylindolin-2-one



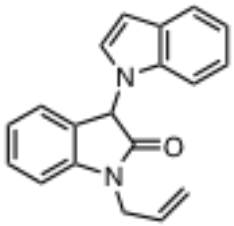
^{1}H NMR (500 MHz, $CDCl_3$) 7.53 (m, 1H), 7.42 (dt, *J* = 9.2, 1.8 Hz, 2H), 7.36 (dt, *J* = 8.3, 1.8 Hz, 2H), 7.29 (m, 1H), 7.17 (m, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.98 (m, 4H), 6.95 (td, *J* = 7.5, 0.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 3.2 Hz, 1H), 5.90 (s, 1H)**. ^{13}C NMR (126 MHz, $CDCl_3$)** 170.68, 142.79, 135.12, 132.91, 128.96, 128.88, 128.71, 128.25, 127.37, 126.23, 125.34, 124.91, 124.27, 123.35, 122.72, 121.14, 120.22, 119.07, 108.98, 108.64, 102.05, 57.70. **HRMS** Calculated ($C_{22}H_{16}N_2O$-H) 323.1190 Found 323.1416

2-8c) 3-(1H-indol-1-yl)-1-(4-nitrophenyl)indolin-2-one



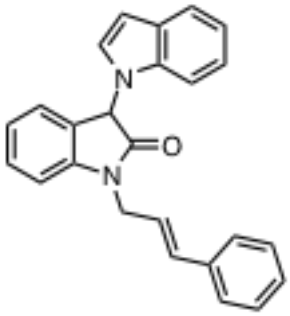
^{1}H NMR (500 MHz, $CDCl_3$) 8.31 (m, 2H), 7.63 (m, 2H), 7.57 (m, 1H), 7.32 (m, 1H), 7.21 (m, 1H), 6.99 (m, 6H), 6.55 (dd, *J* = 3.3, 0.6 Hz, 1H), 6.02 (s, 1H)**. ^{13}C NMR (126 MHz, $CDCl_3$)** 170.48, 145.60, 141.23, 138.70, 135.14, 129.29, 128.31, 125.95, 125.36, 124.89, 124.12, 123.73, 123.28, 121.40, 120.43, 119.36, 109.02, 108.44, 102.51, 57.61. **HRMS** Calculated ($C_{22}H_{15}N_3O_3$-H) 368.1035 Found 368.1065

2-8d) 1-allyl-3-(1H-indol-1-yl)indolin-2-one ^{1}H NMR



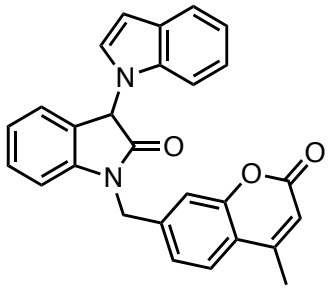
^{1}H NMR (500 MHz, $CDCl_3$) 7.52 (m, 1H), 7.28 (ddd, *J* = 8.8, 2.0, 1.0 Hz, 1H), 6.98 (m, 4H), 6.87 (m, 3H), 6.49 (d, *J* = 3.2 Hz, 1H), 5.76 (m, 2H), 5.19 (m, 2H), 4.30 (m, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** 171.16, 142.03, 135.22, 129.95, 129.00, 128.15, 125.84, 124.07, 123.58, 122.23, 121.09, 120.19, 119.05, 117.29, 108.64, 108.63, 102.06, 57.32, 41.70. **HRMS** Calculated ($C_{19}H_{16}N_2O$-H) 279.1190 Found 279.1185

2-8e) 1-cinnamyl-3-(1H-indol-1-yl)indolin-2-one ^{1}H NMR



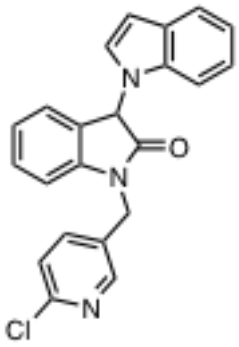
^{1}H NMR (500 MHz, $CDCl_3$) 7.57 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.27 (m, 3H), 7.22 (m, 2H), 7.19 (dd, *J* = 5.0 3.6 Hz, 1H), 7.10 (m, 1H), 6.99 (m, 3H), 6.97 (dd, *J* = 9.6, 5.1 Hz, 3H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.51 (d, *J* = 3.2 Hz, 1H), 6.17 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.85 (s, 1H), 4.51 (dd, *J* = 6.1, 1.0 Hz, 2H). **^{13}C NMR (126 MHz, $CDCl_3$)** 171.24, 142.03, 135.18, 134.96, 132.74, 129.10, 128.21, 127.63, 127.07, 126.01, 125.47, 124.16, 123.64, 122.30, 121.19, 121.12 120.23, 119.08, 108.69, 108.62, 102.08, 57.48, 41.34. **HRMS** Calculated ($C_{25}H_{20}N_2O$-H) 363.1497 Found 363.1366

2-8f) 3-(1H-indol-1-yl)-1-((4-methyl-2-oxo-2H-chromen-7-yl)methyl)indolin-2-one



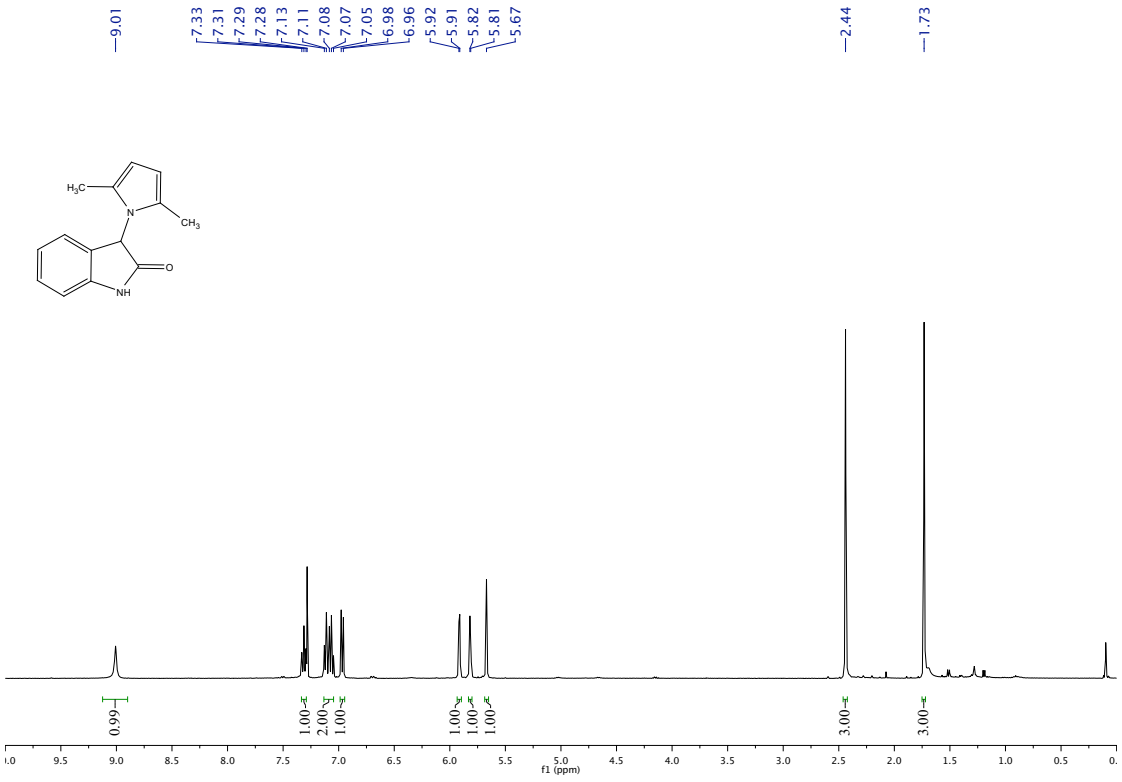
^{1}H NMR (500 MHz, $CDCl_3$) 7.56 (dd, *J* = 6.7, 2.7 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.19 (m, 3H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.02 (m, 2H), 6.91 (m, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.49 (m, 1H), 6.21 (d, *J* = 1.2 Hz, 1H), 5.92 (s, 1H), 4.97 (dd, *J* = 35.6, 15.9 Hz, 2H), 2.33 (d, *J* = 1.2 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.77, 160.49, 153.74, 152.07, 142.54, 139.84, 136.25, 130.24, 129.28, 126.97, 125.50, 125.45, 125.41, 124.55, 123.77, 123.34, 122.22, 121.34, 120.25, 119.64, 115.92, 115.23, 109.72, 109.55, 103.36, 58.46, 43.69, 18.68.

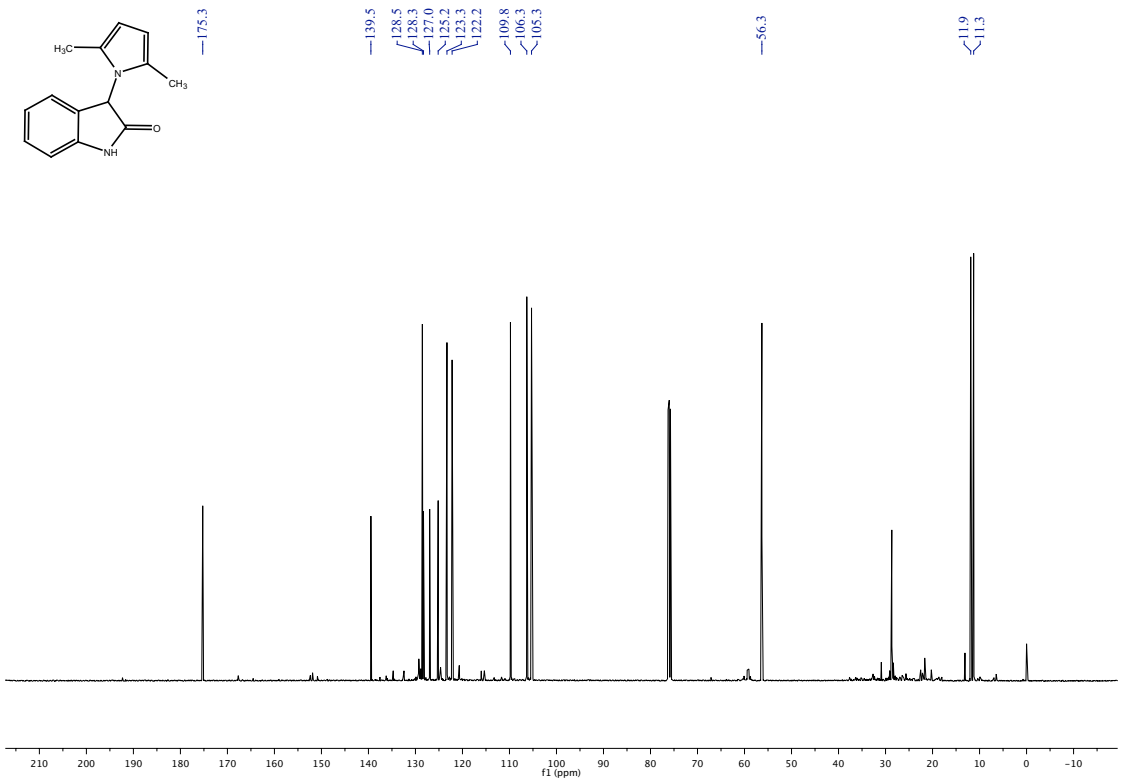
2-8g) 1-((6-chloropyridin-3-yl)methyl)-3-(1H-indol-1-yl)indolin-2-one ^{1}H NMR



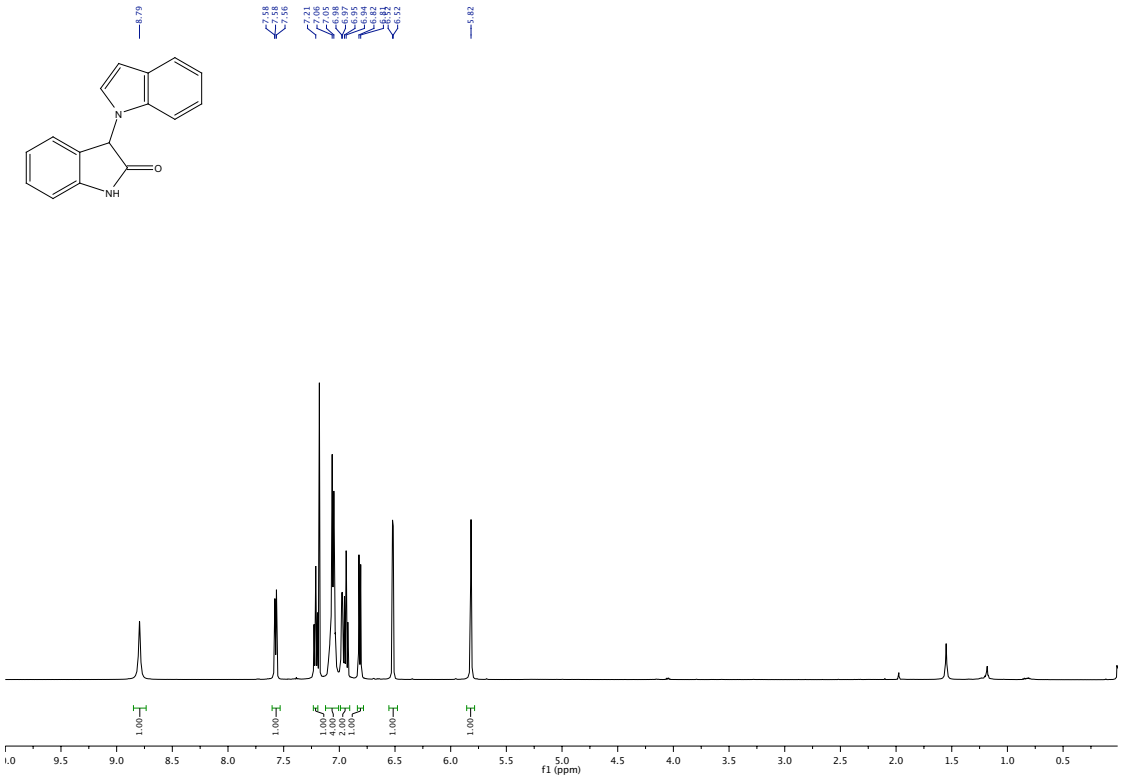
^{1}H NMR (500 MHz, $CDCl_3$) 8.39 (d, *J* = 2.4 Hz, 1H), 7.51 (m, 2H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.84 (m, 5H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.51 (d, *J* = 3.2 Hz, 1H), 5.87 (s, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 172.85, 151.43, 148.97, 142.18, 138.56, 136.13, 130.32, 130.26, 130.13, 129.31, 127.03, 125.61, 125.39, 124.79, 124.50, 123.92, 123.29, 122.25, 121.40, 121.28, 120.31, 120.18, 110.50, 109.70, 109.62, 109.26, 103.38, 103.15, 58.46, 41.02.**HRMS** Calculated ($C_{22}H_{16}ClN_3O$-H) 372.0904 Found 372.0867

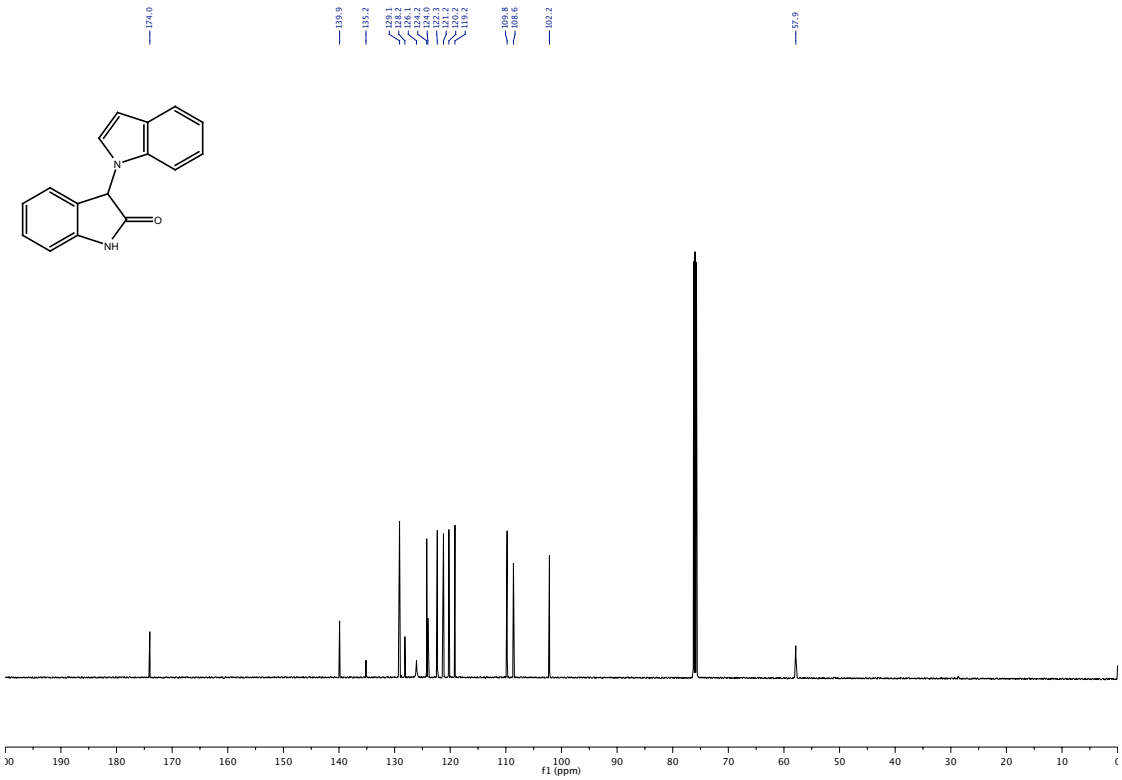
NMR SPECTRA
NMR Spectra for Compound 2-1b



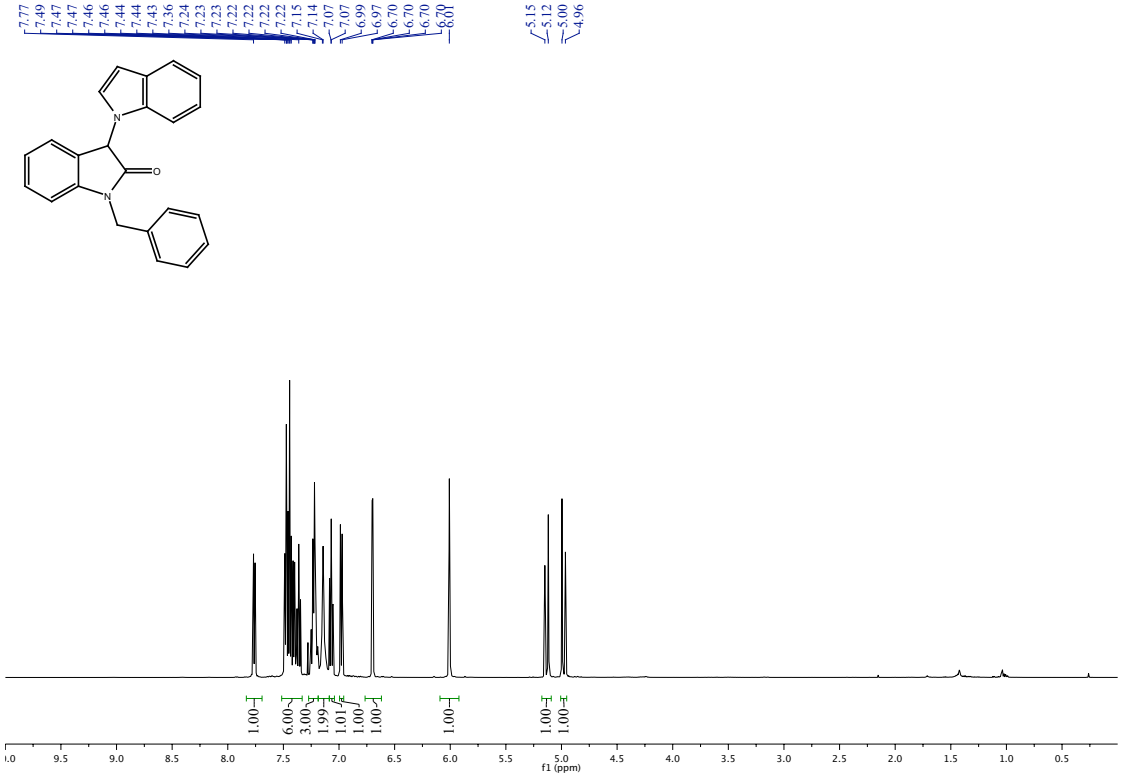


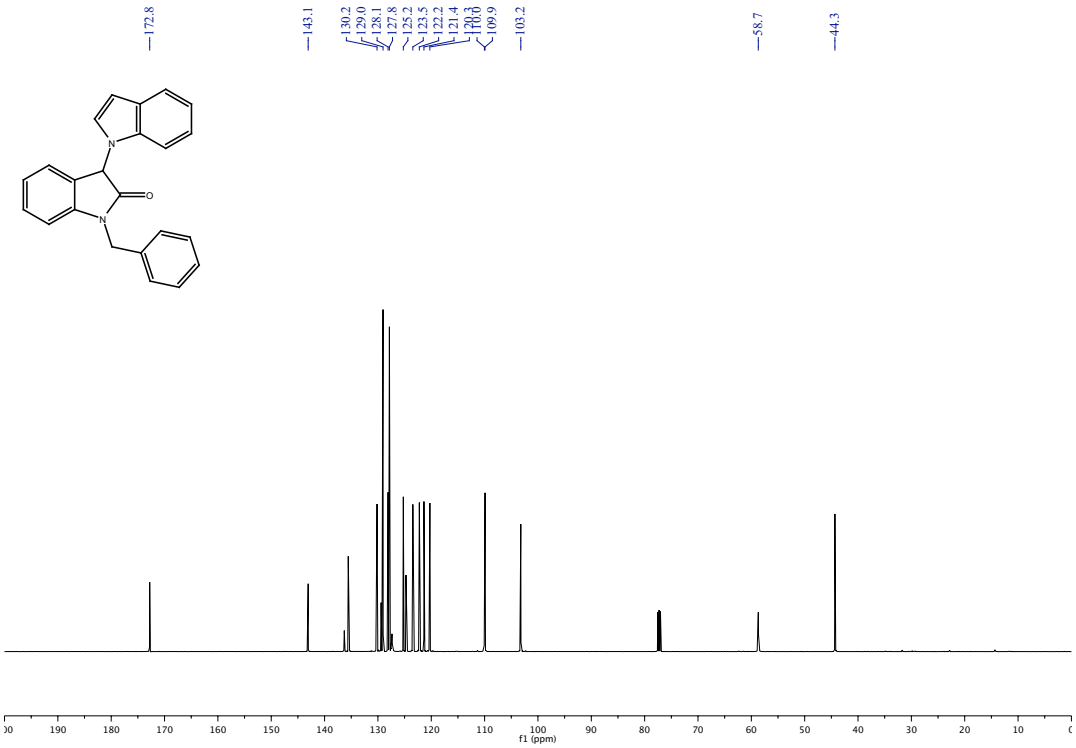
NMR Spectra for Compound 2-3c





NMR Spectra for Compound 2-3d





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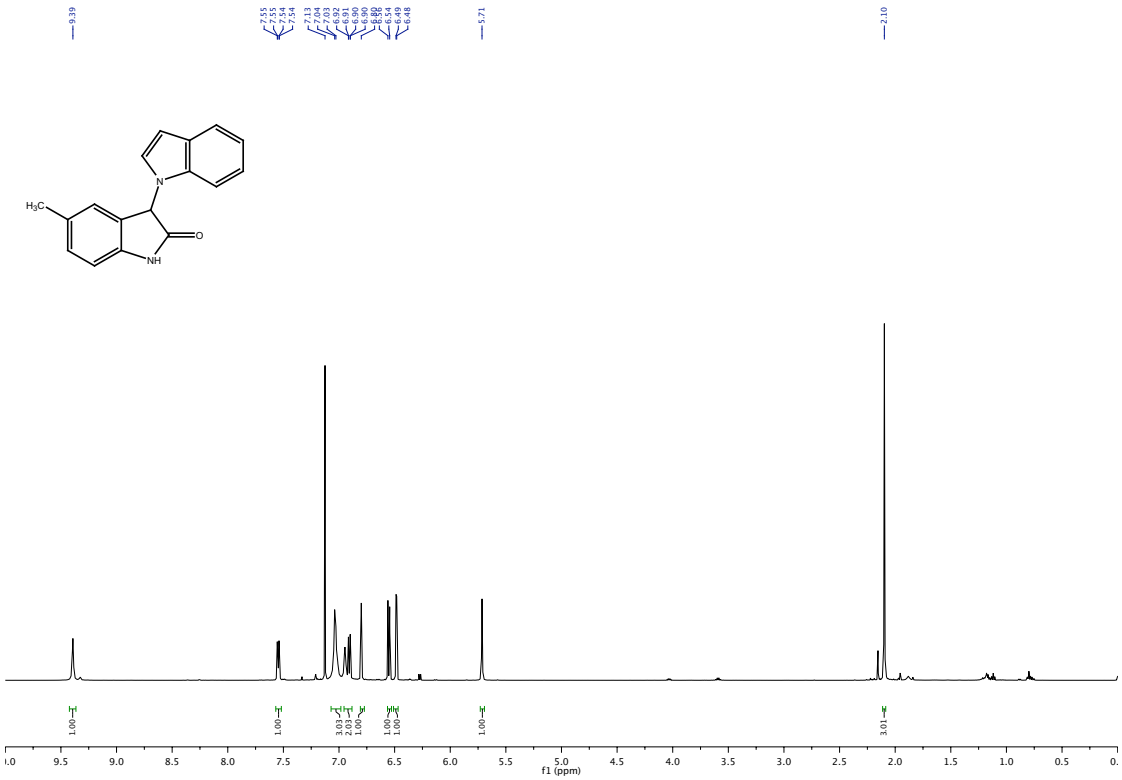

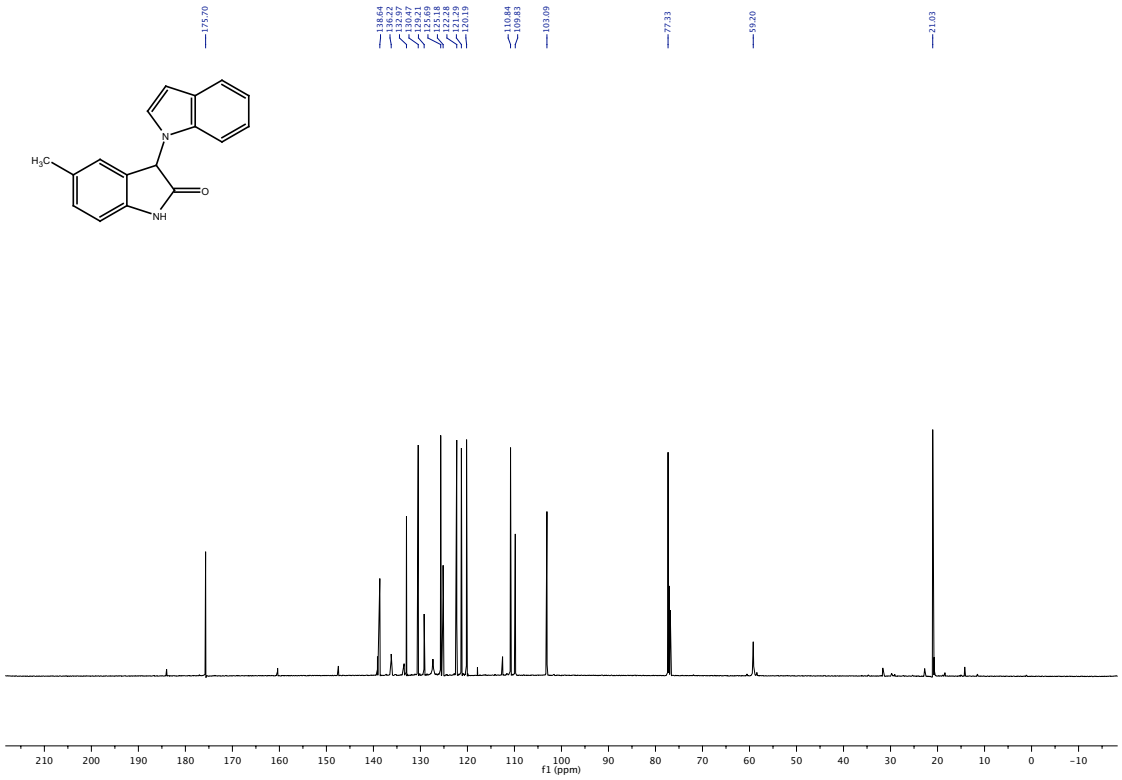

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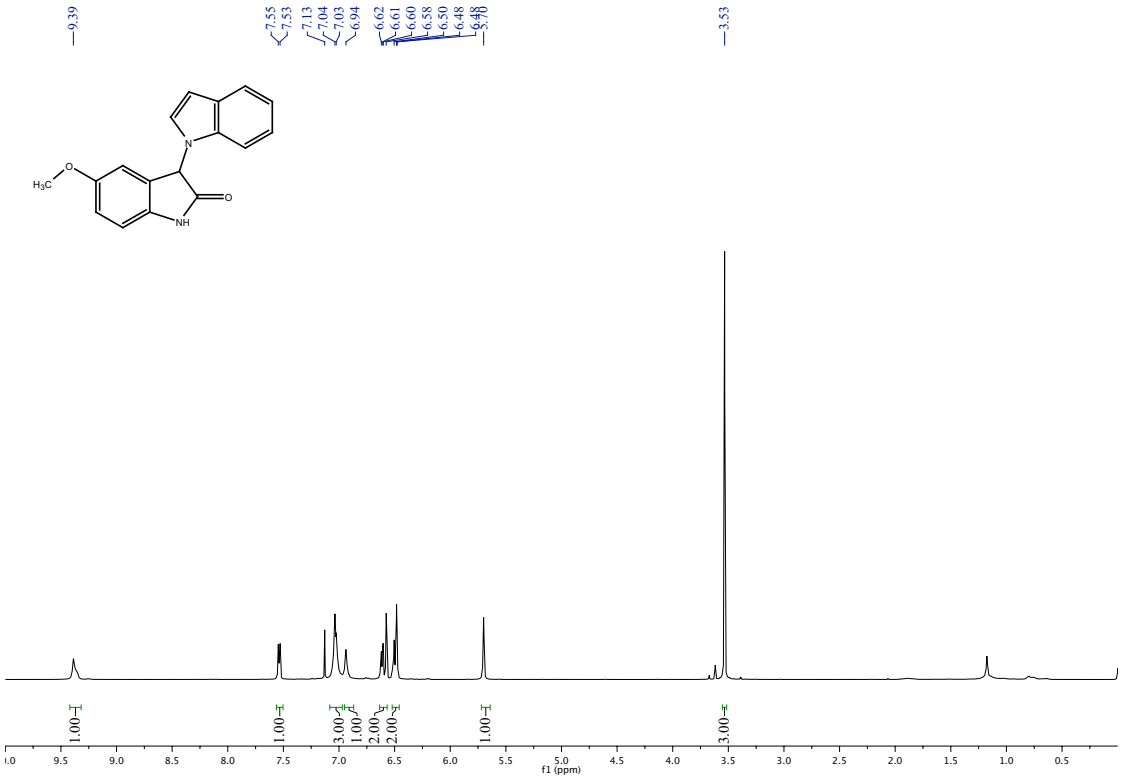

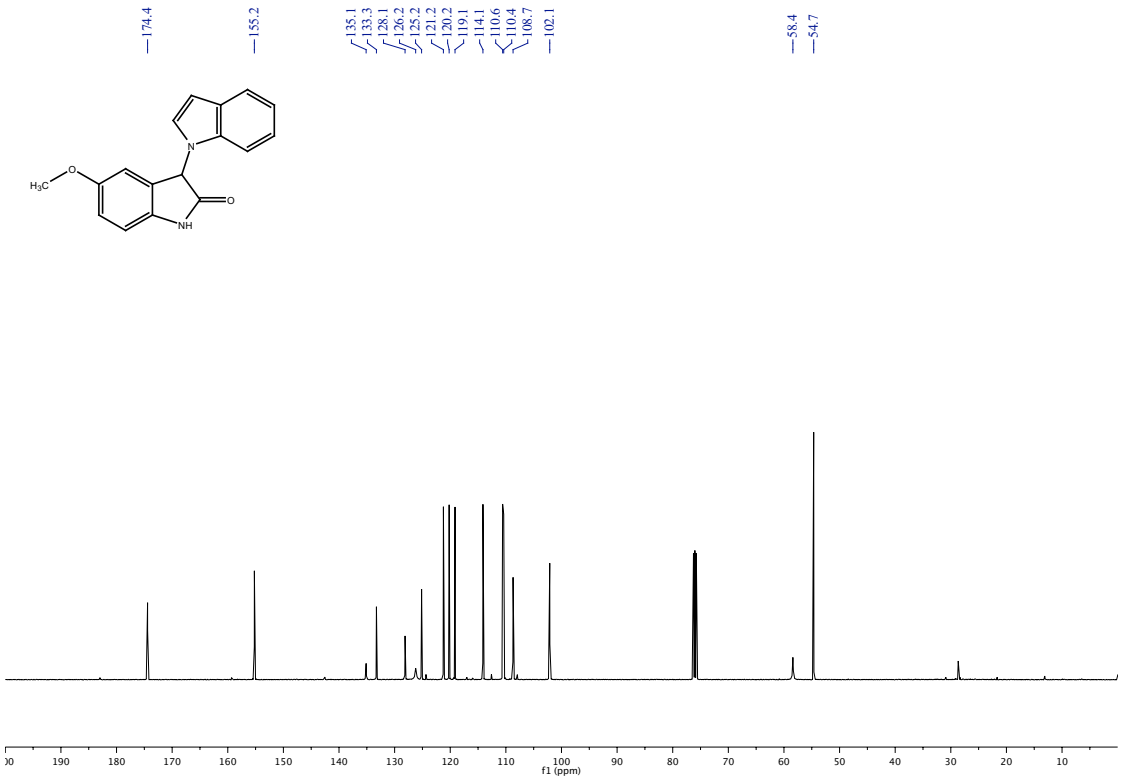

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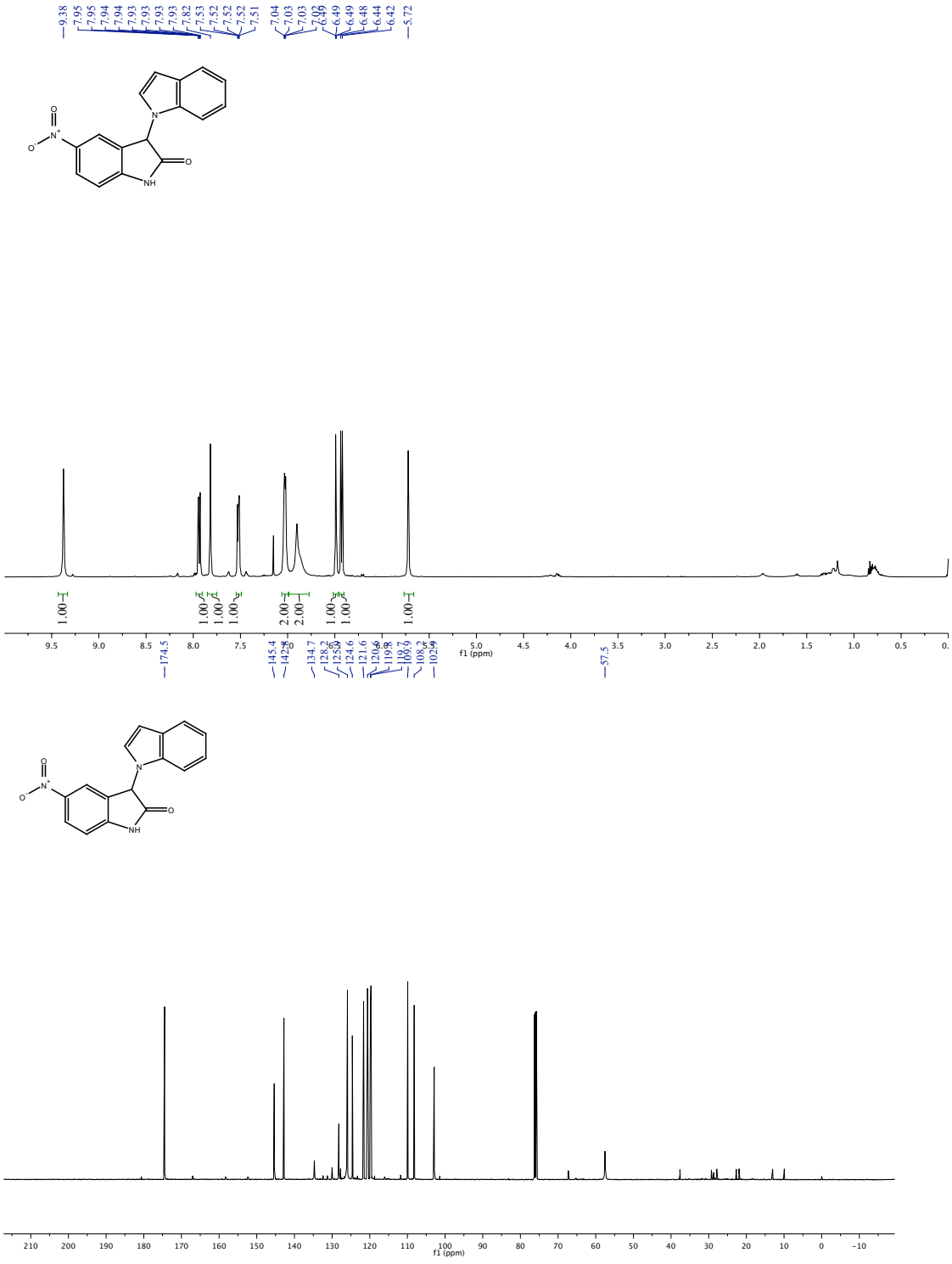

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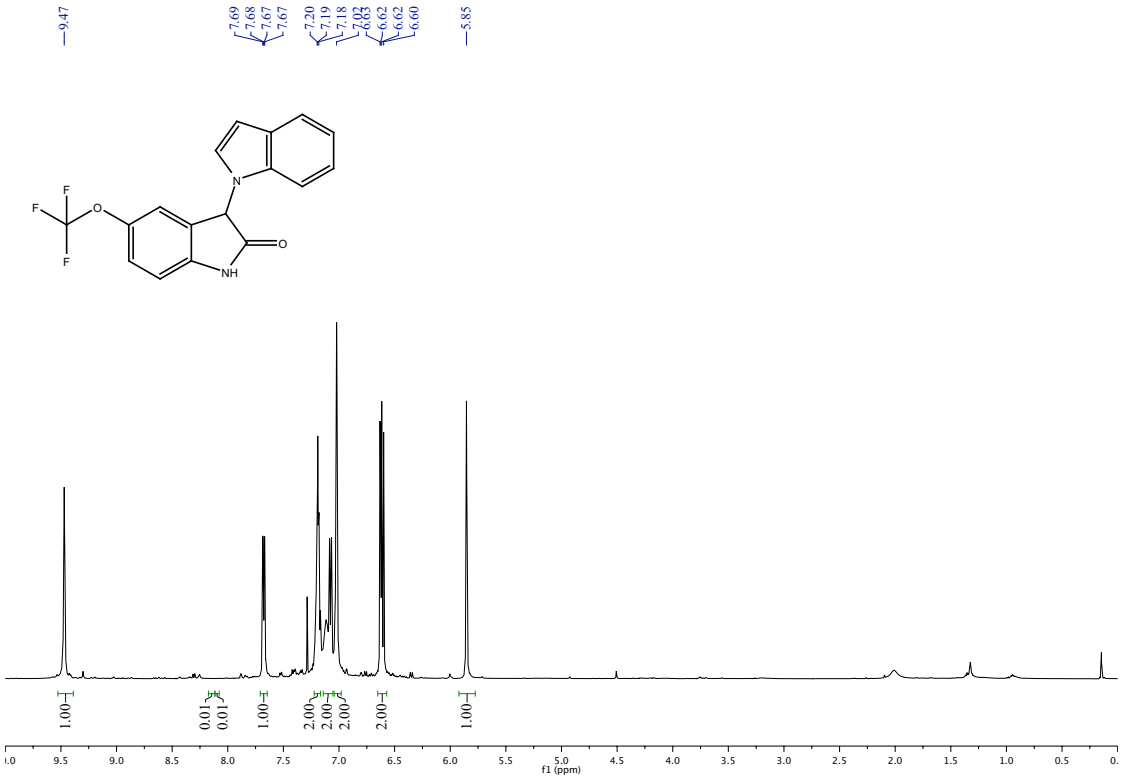

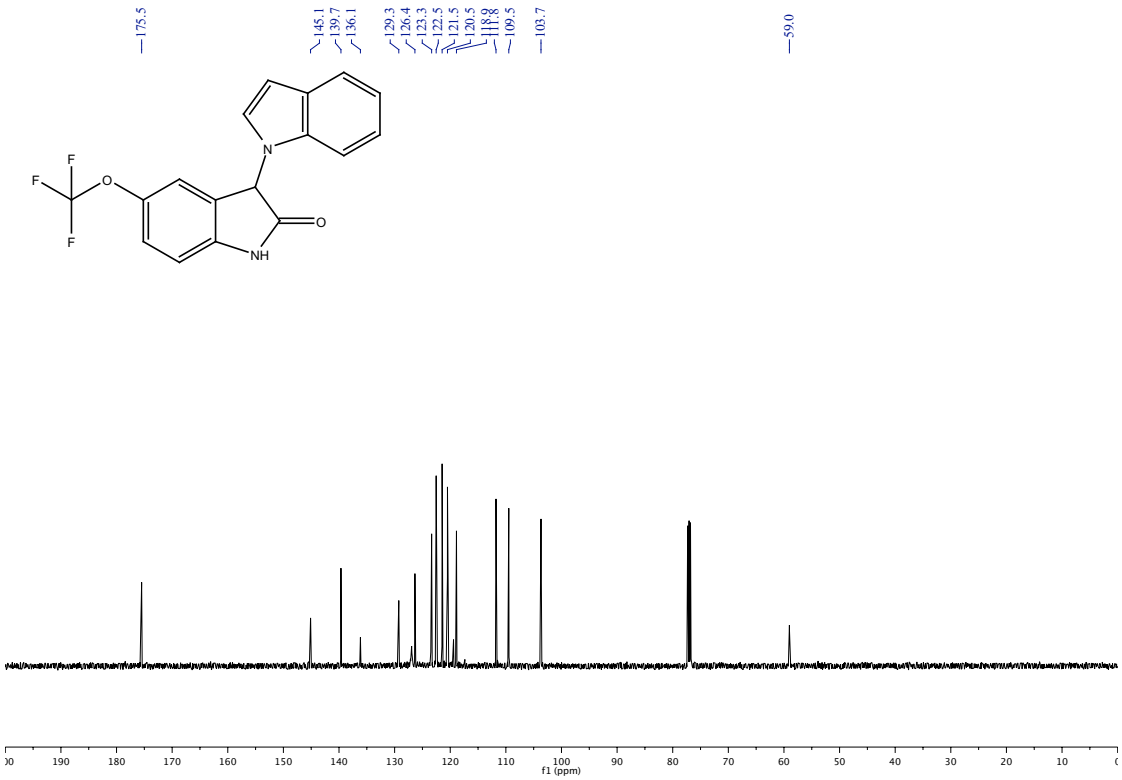

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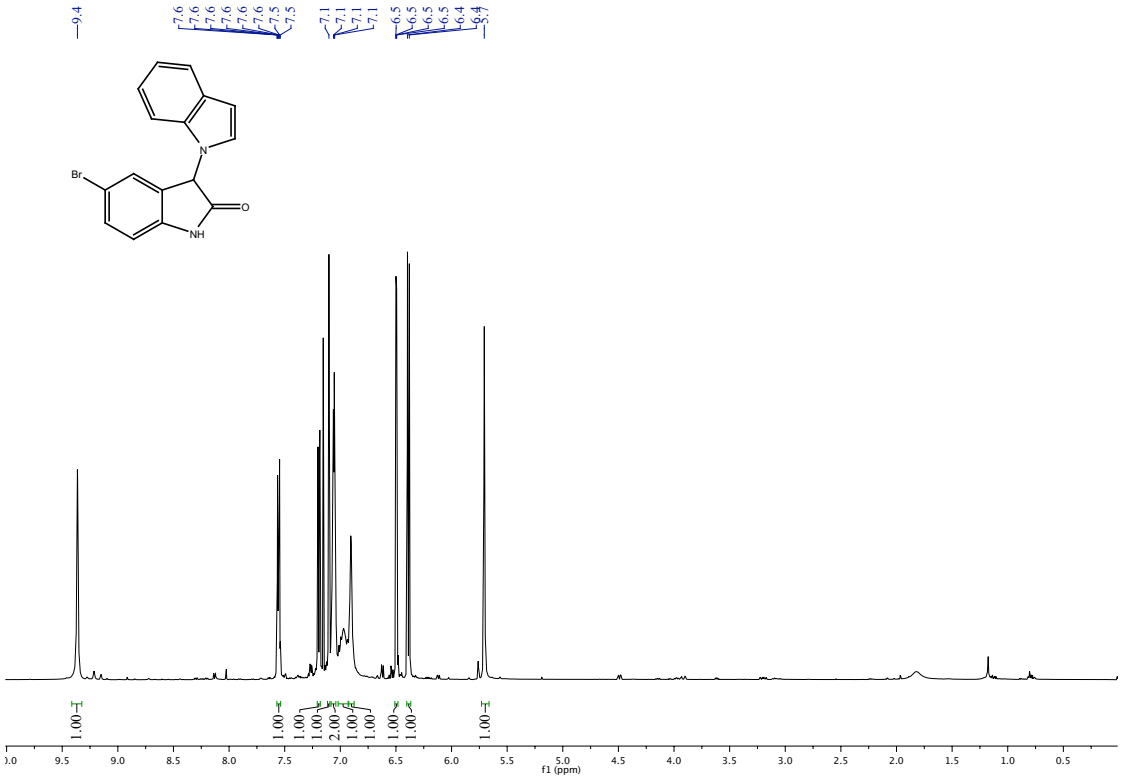

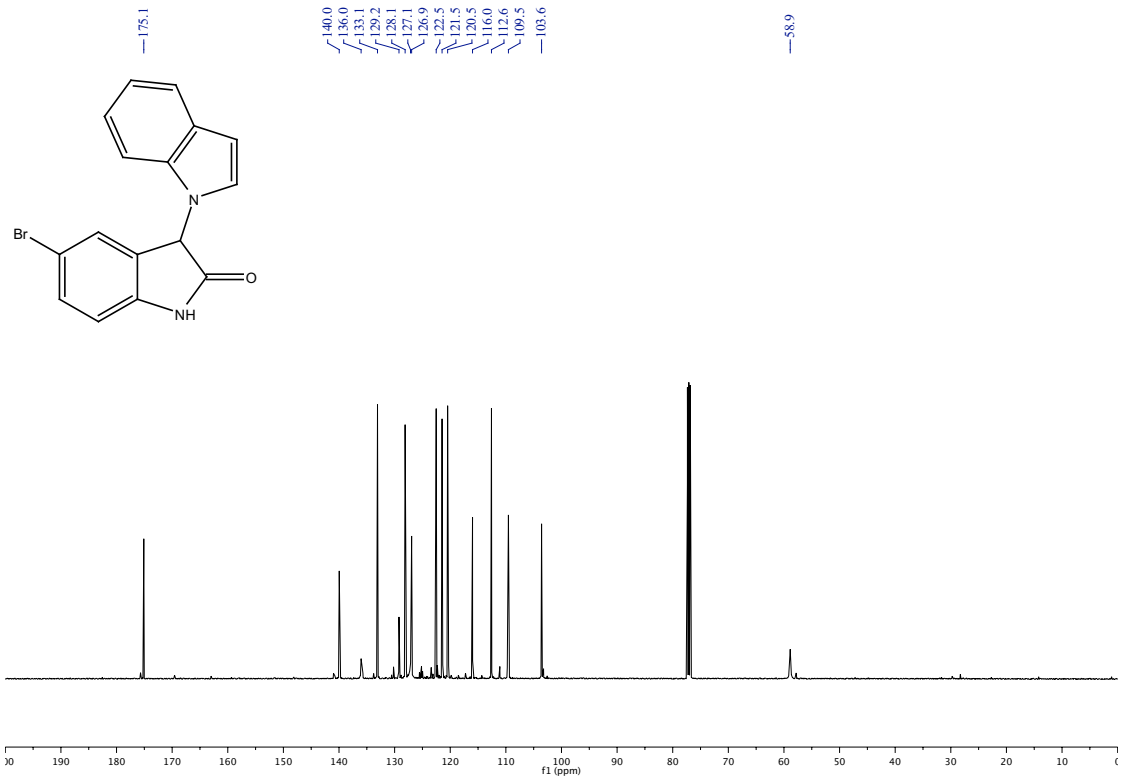

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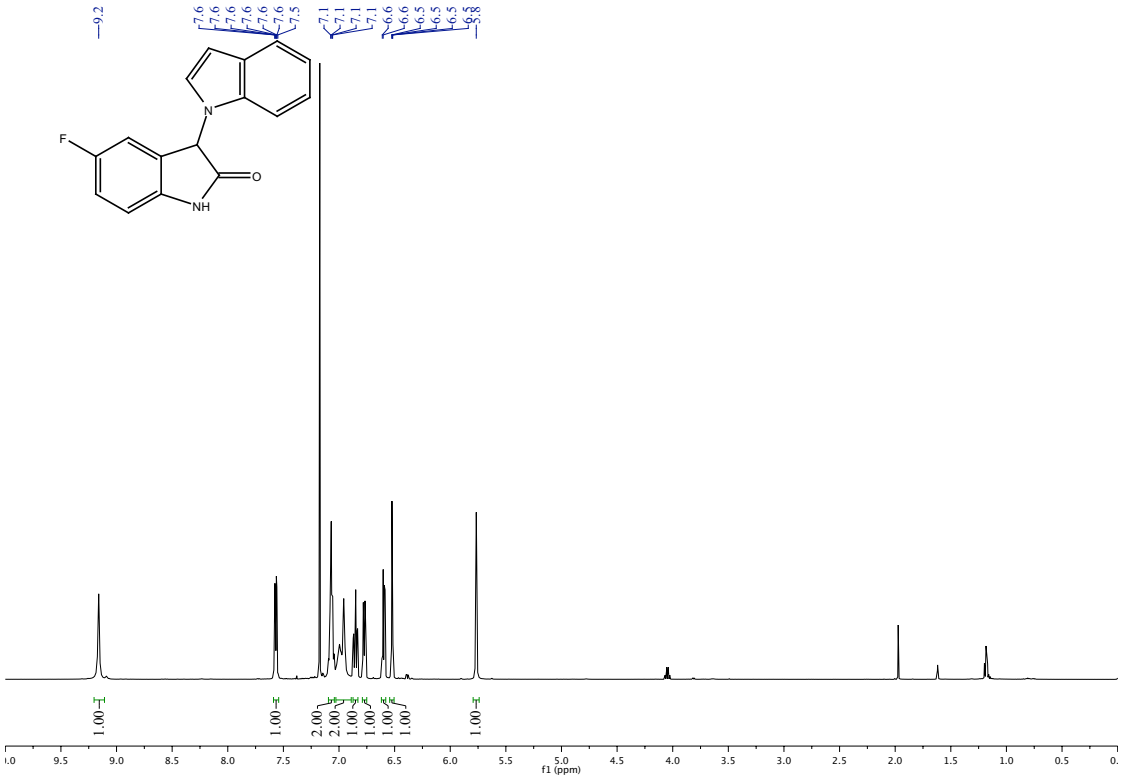

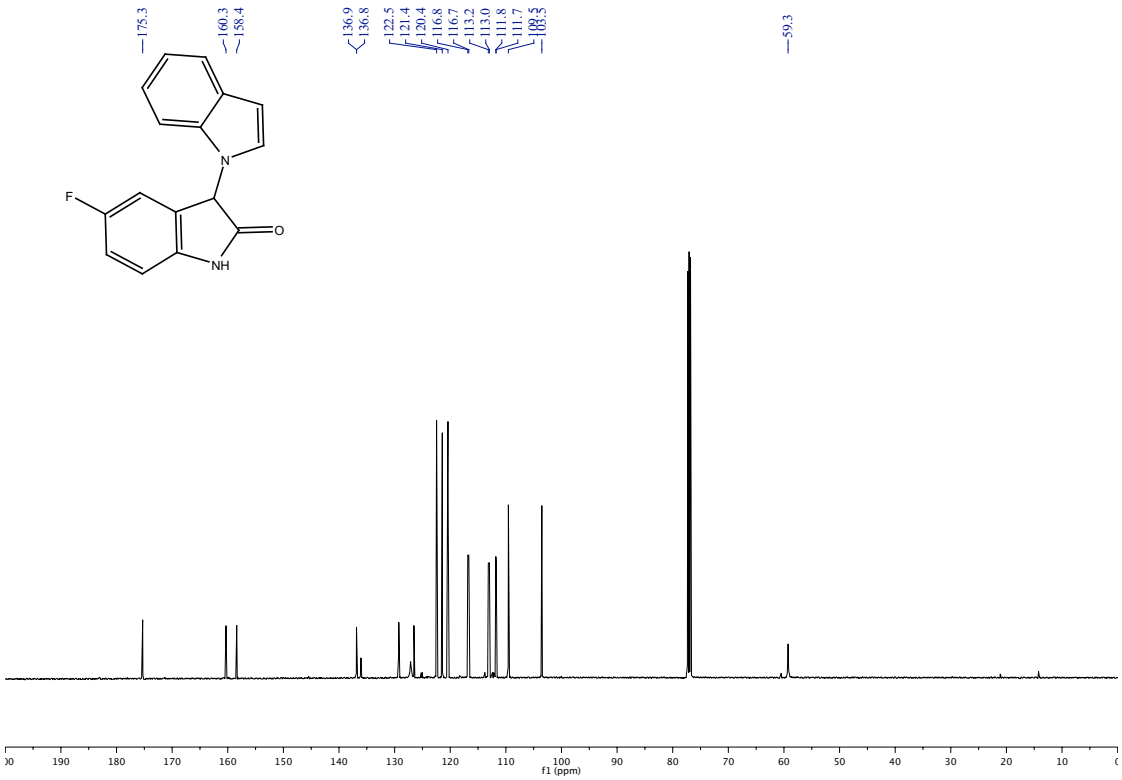

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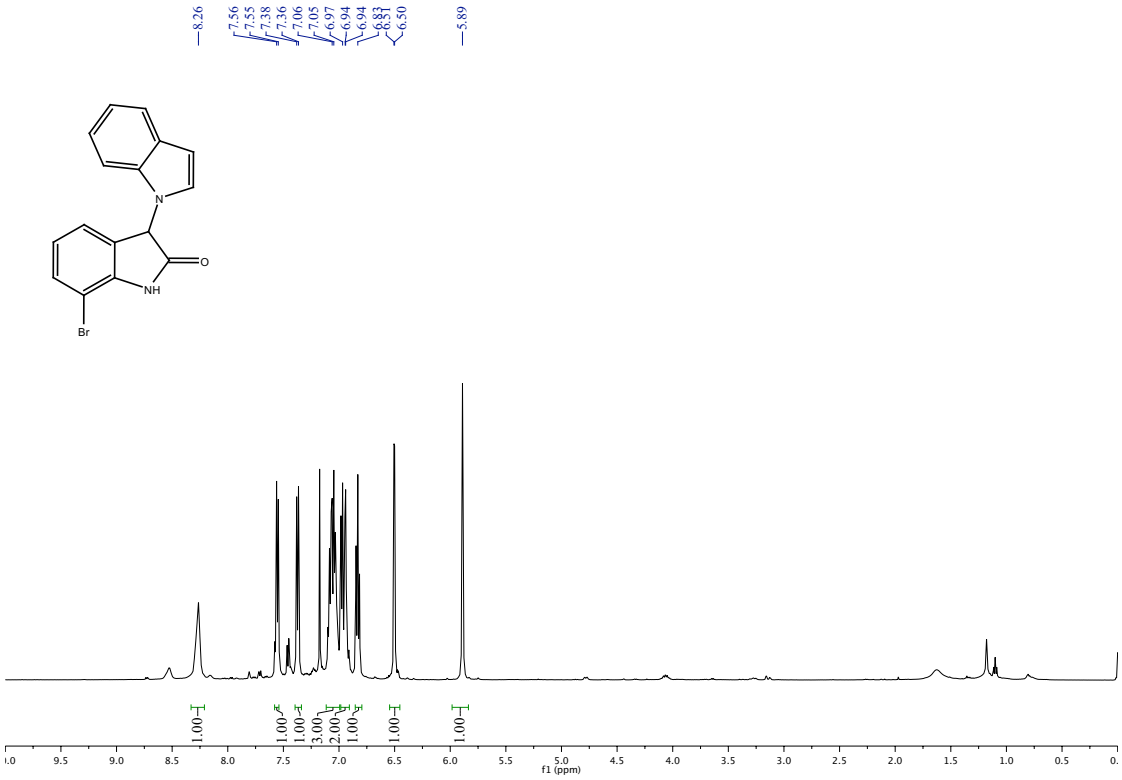

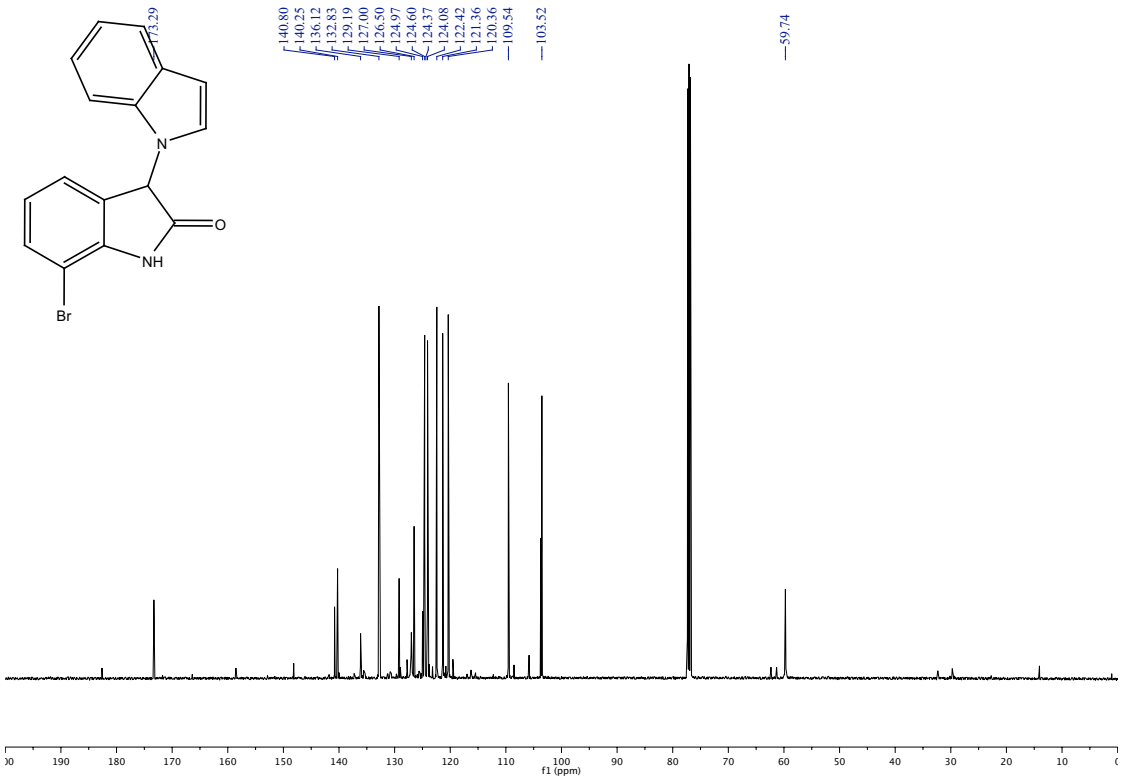

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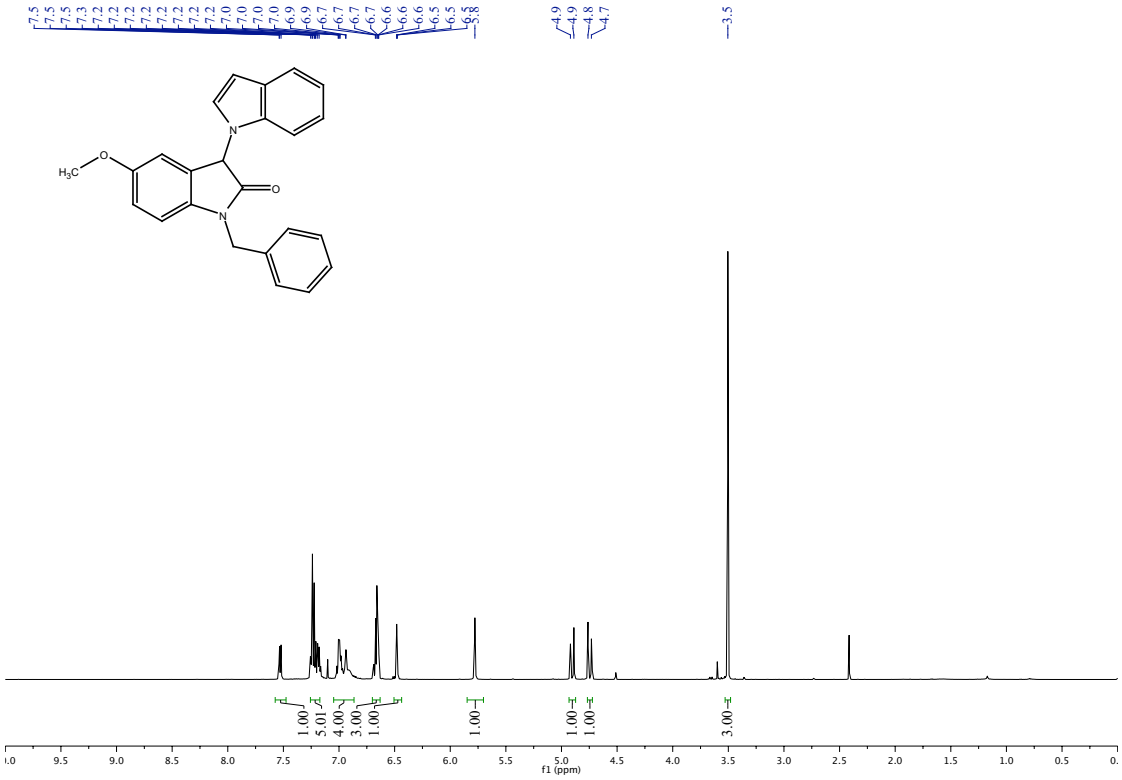

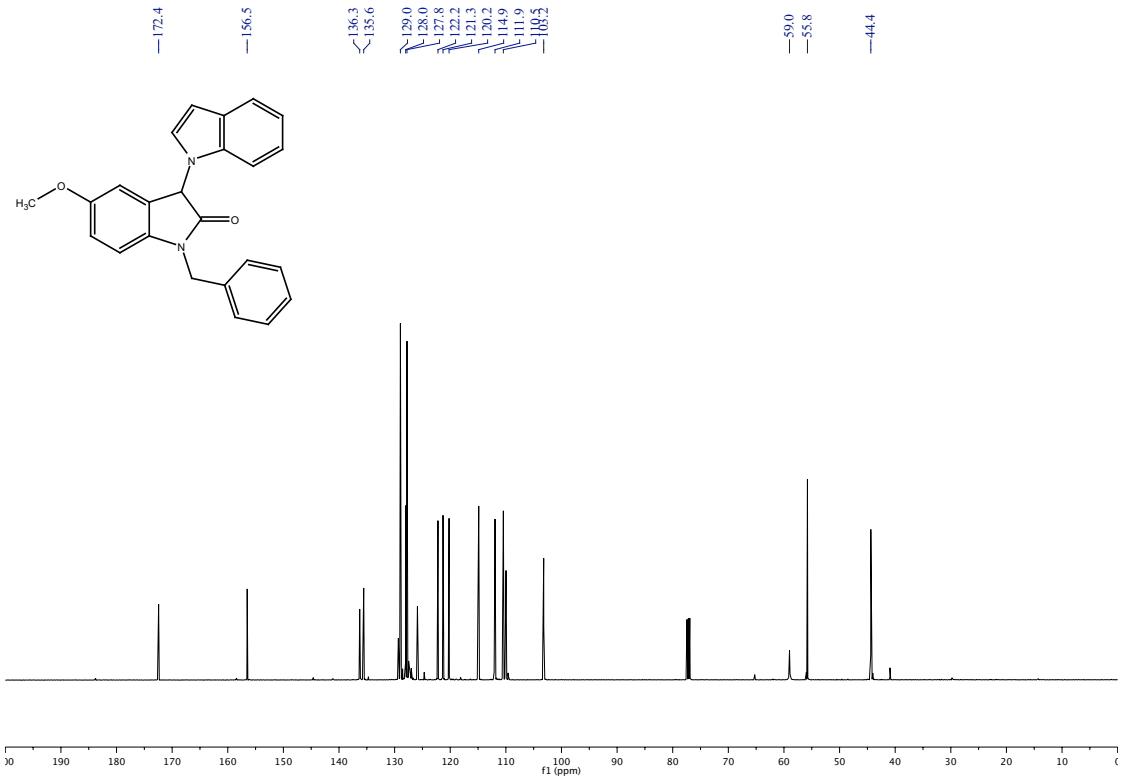

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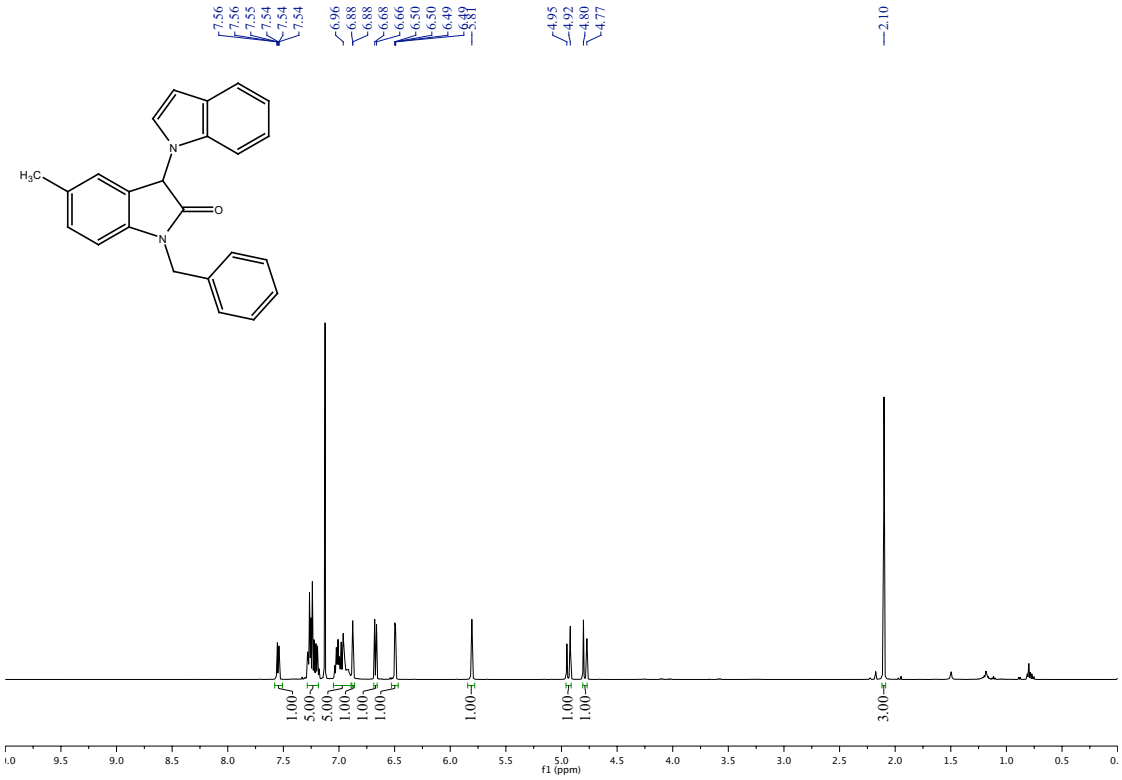

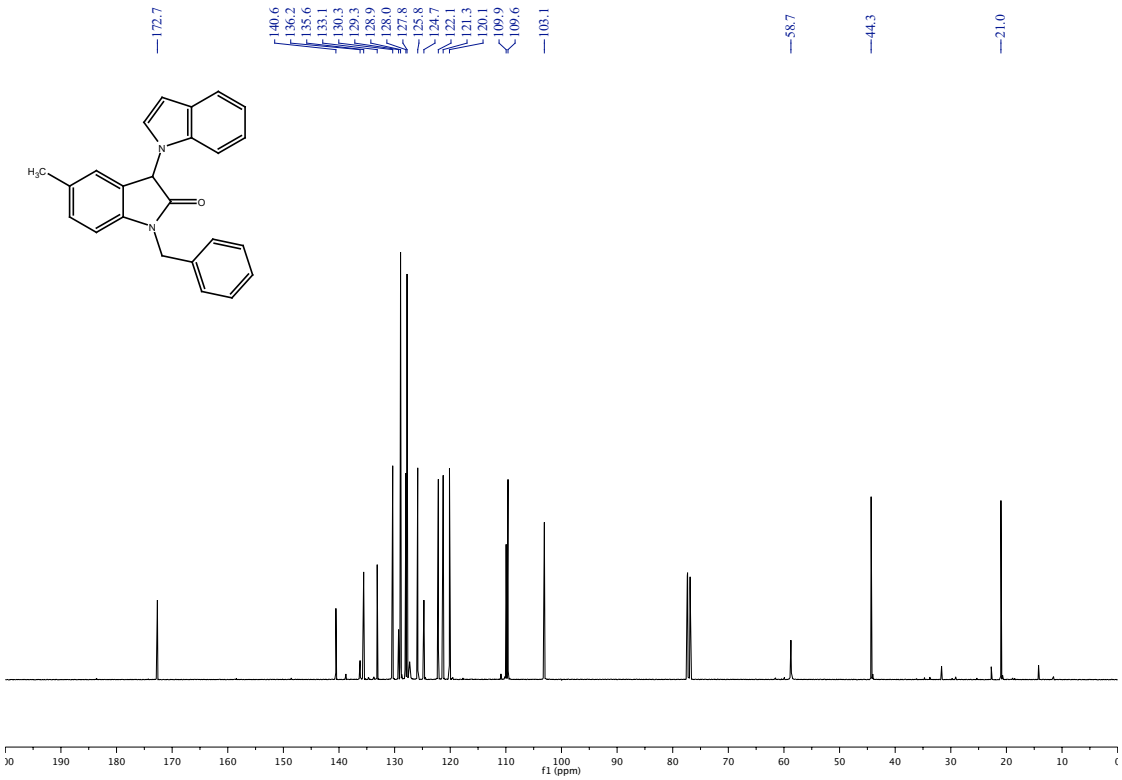

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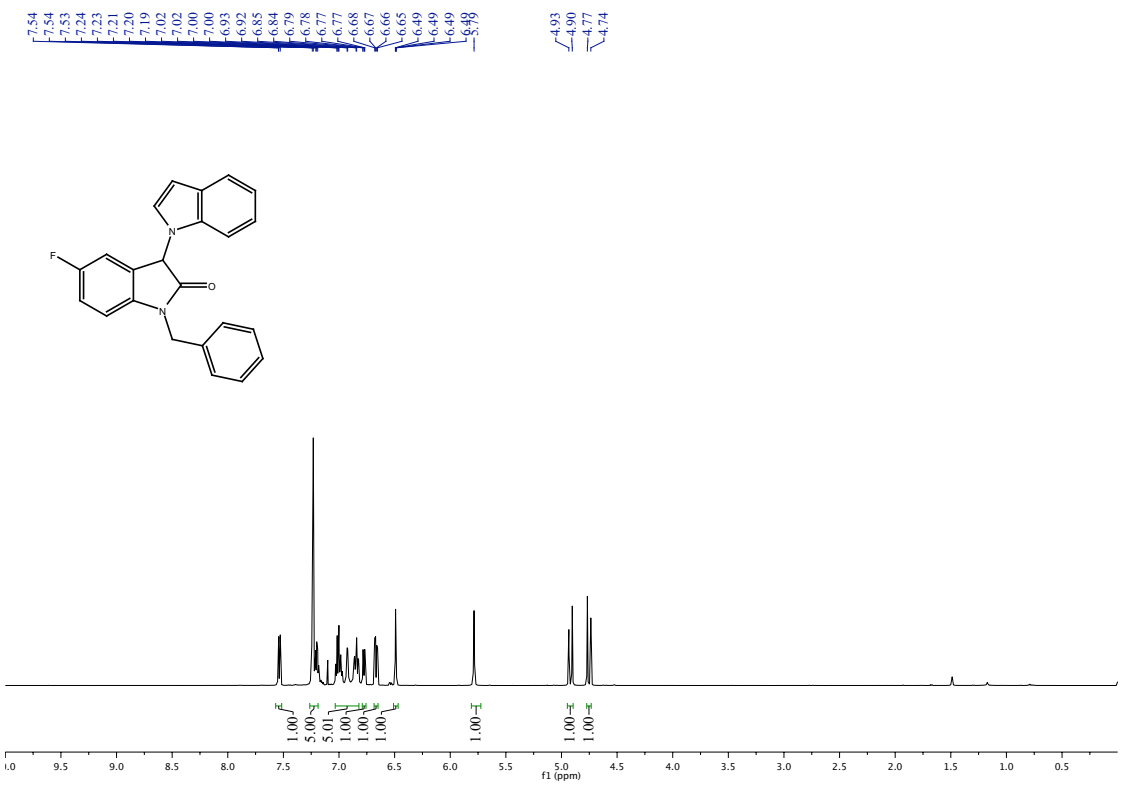

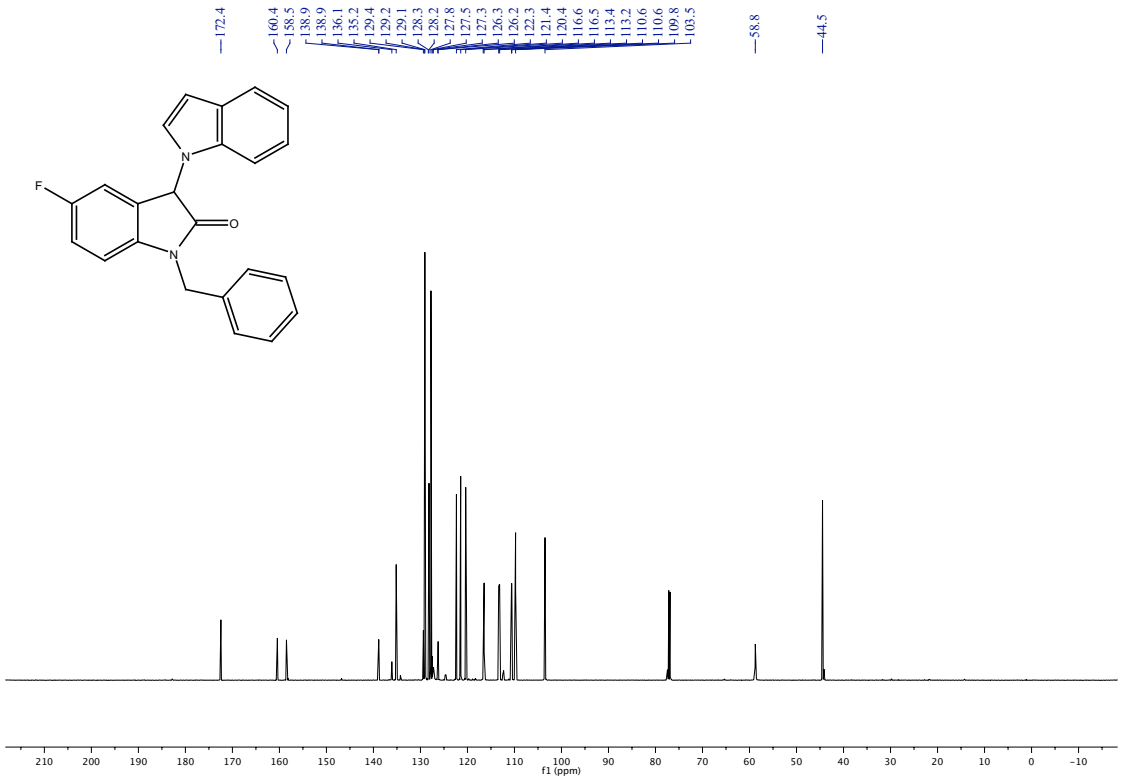

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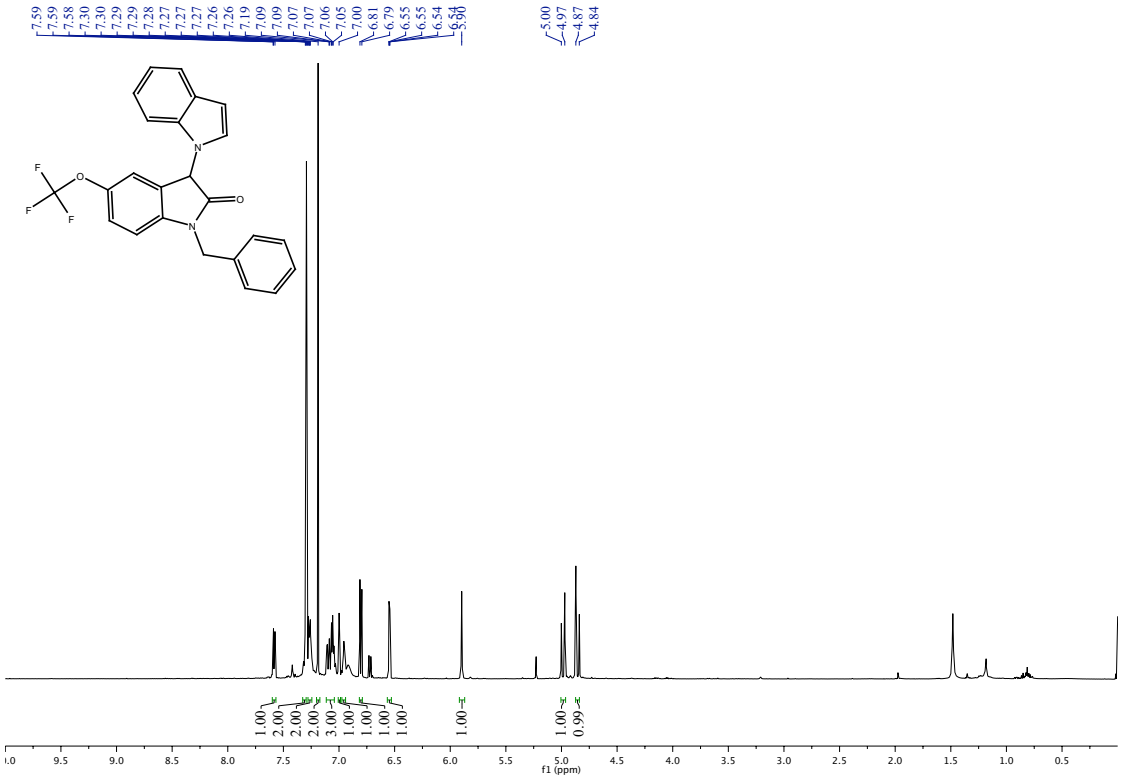

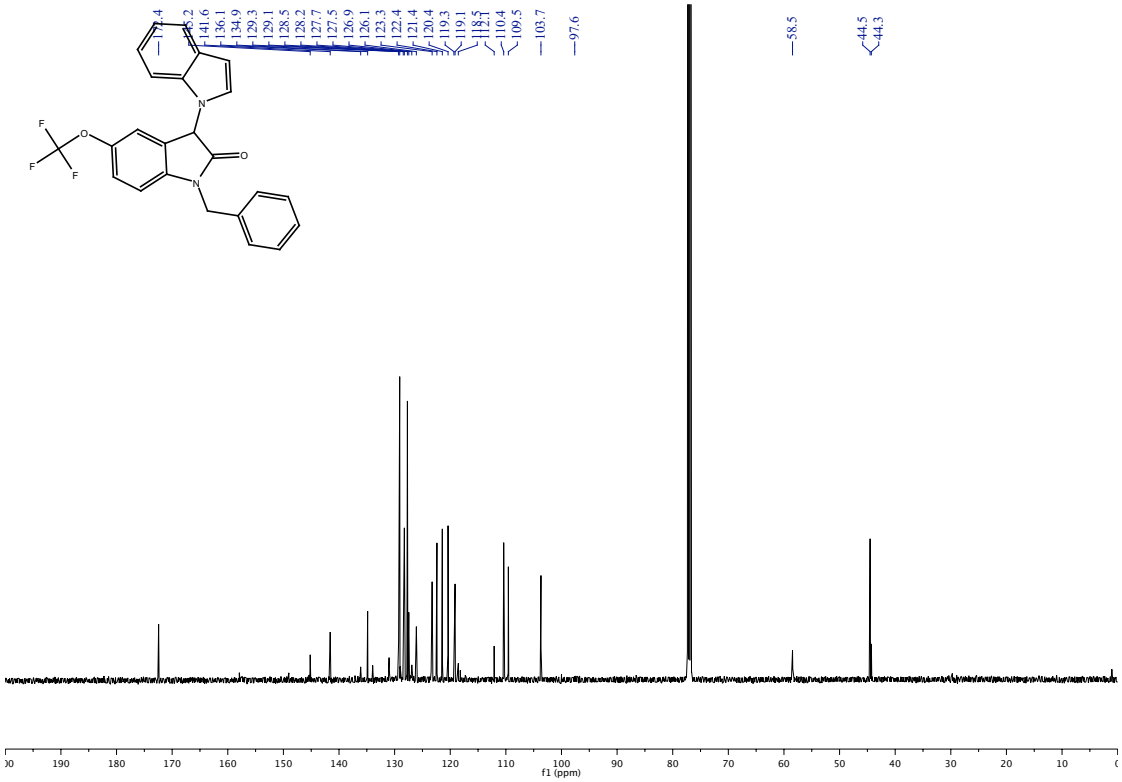

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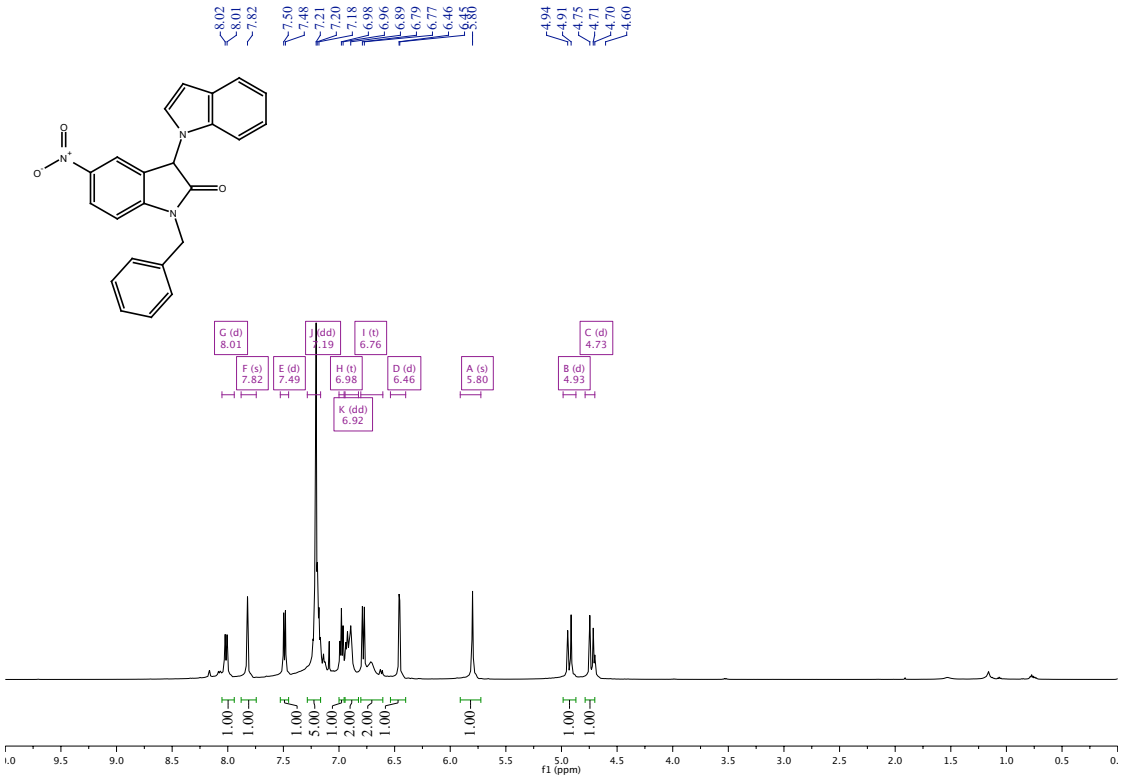

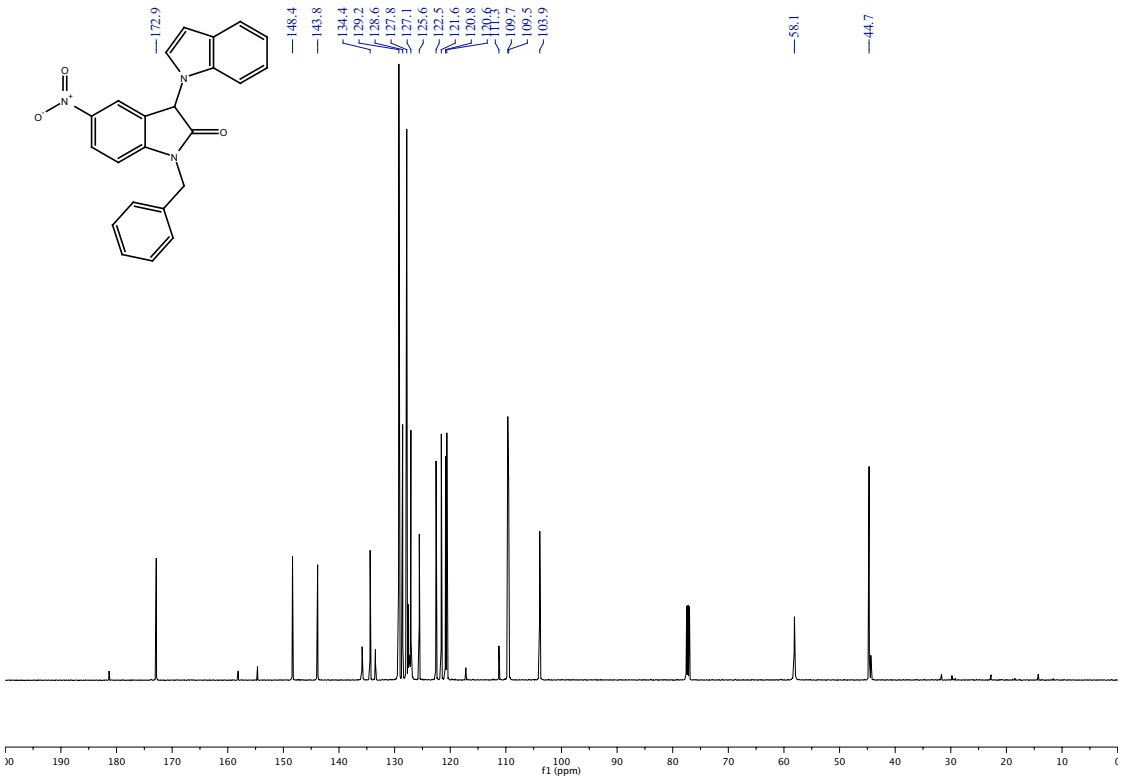

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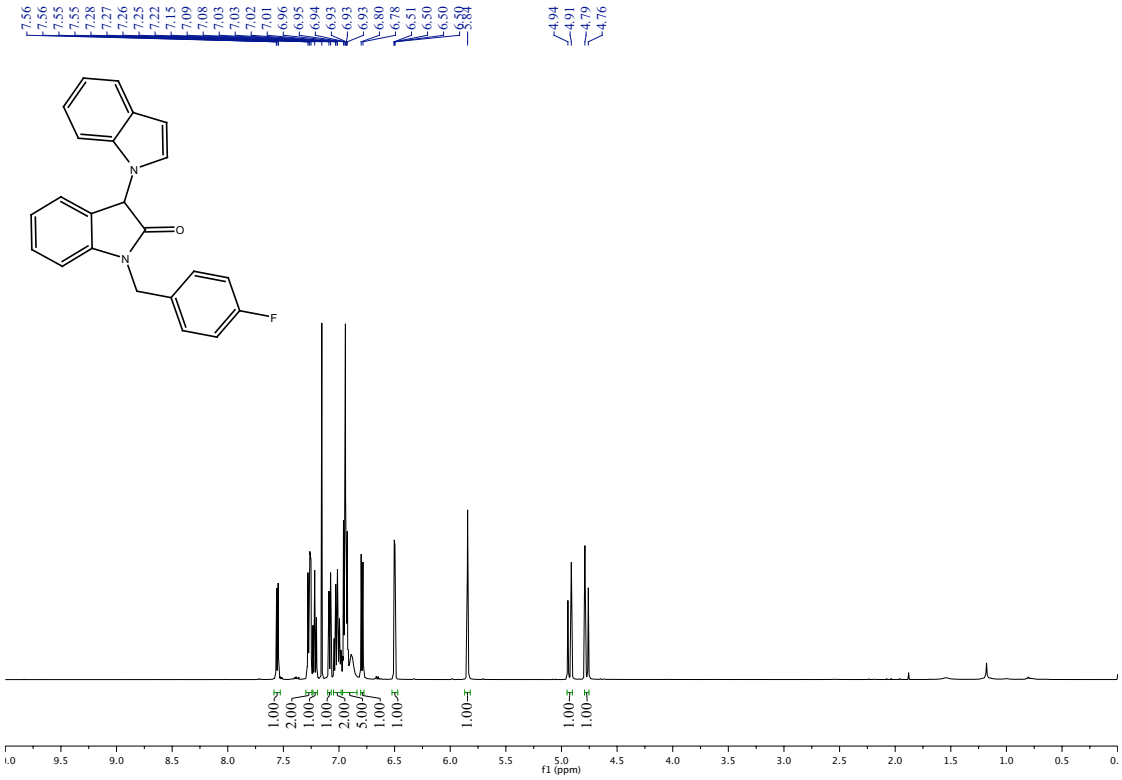

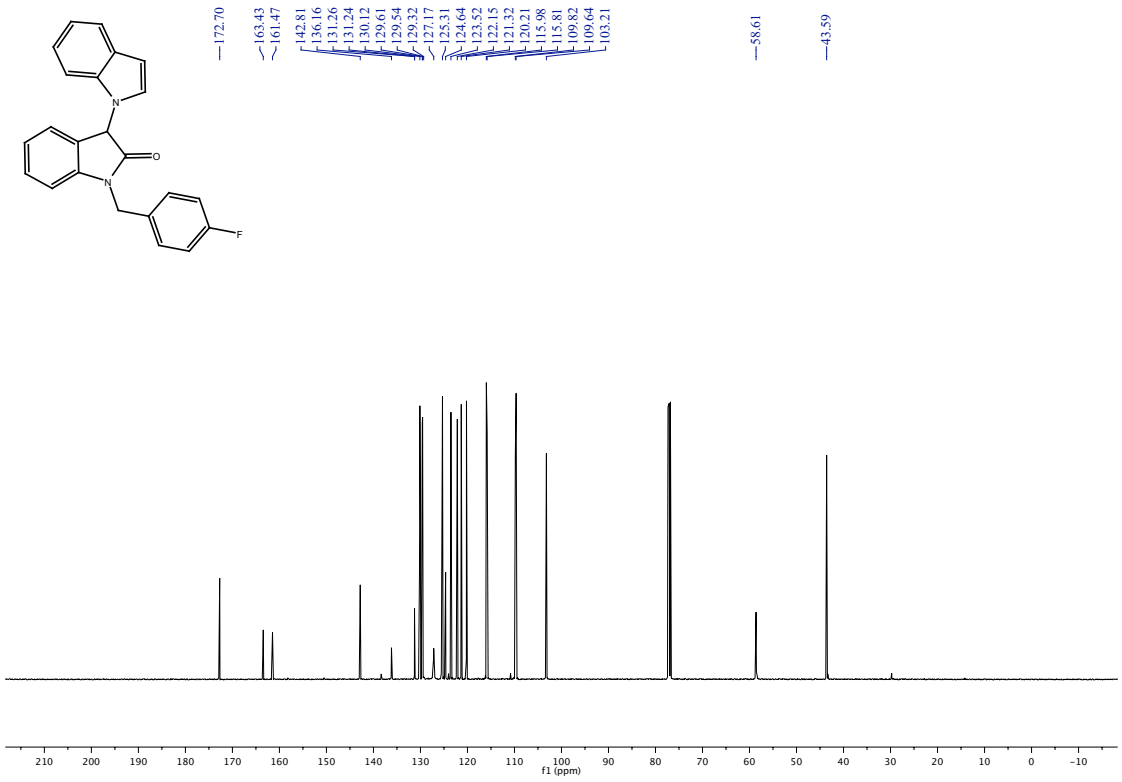

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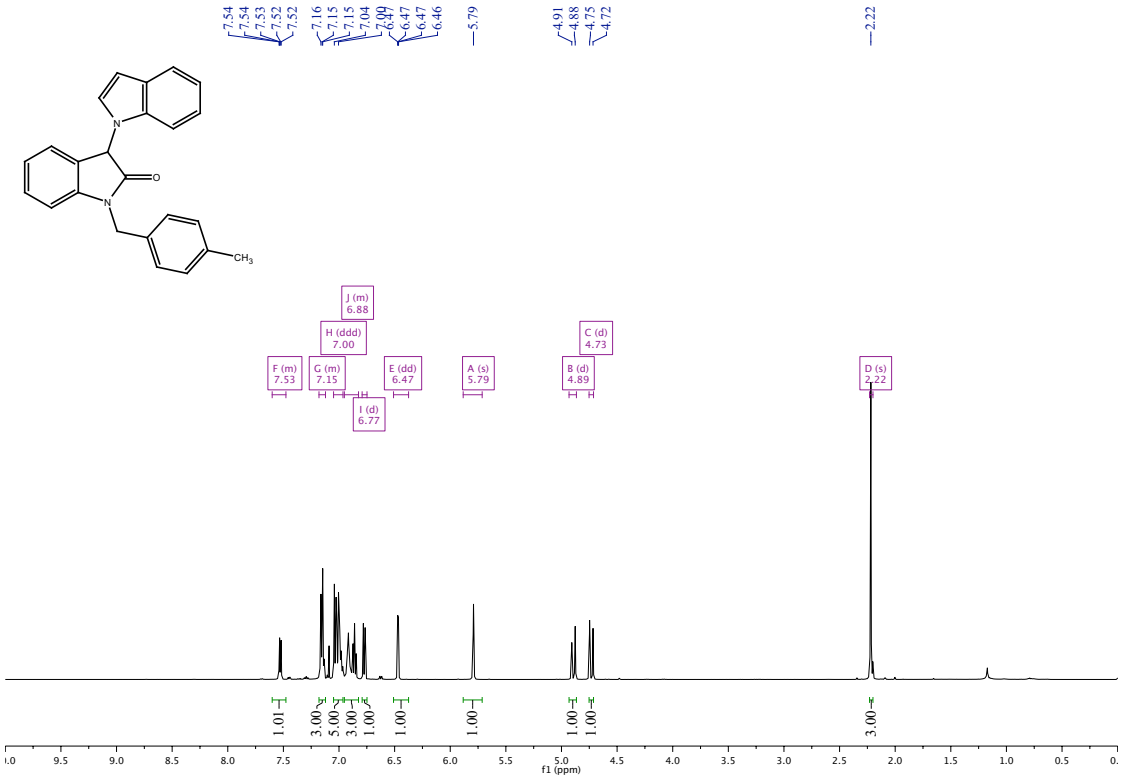

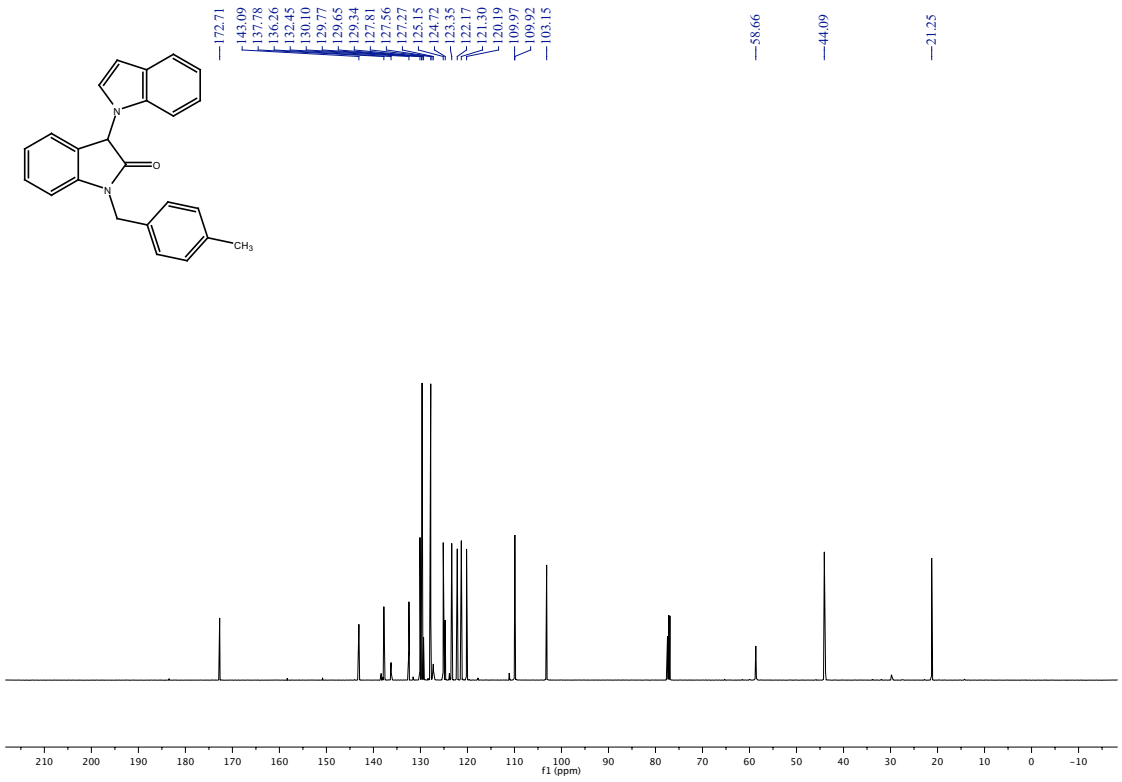

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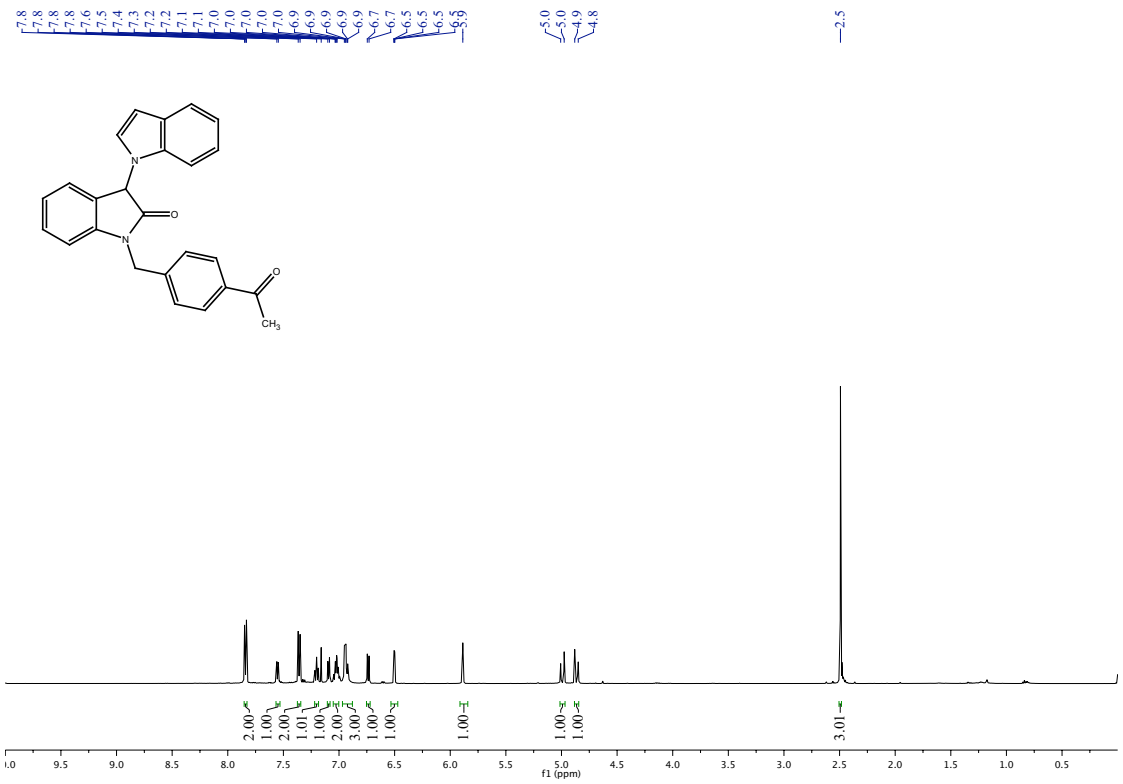

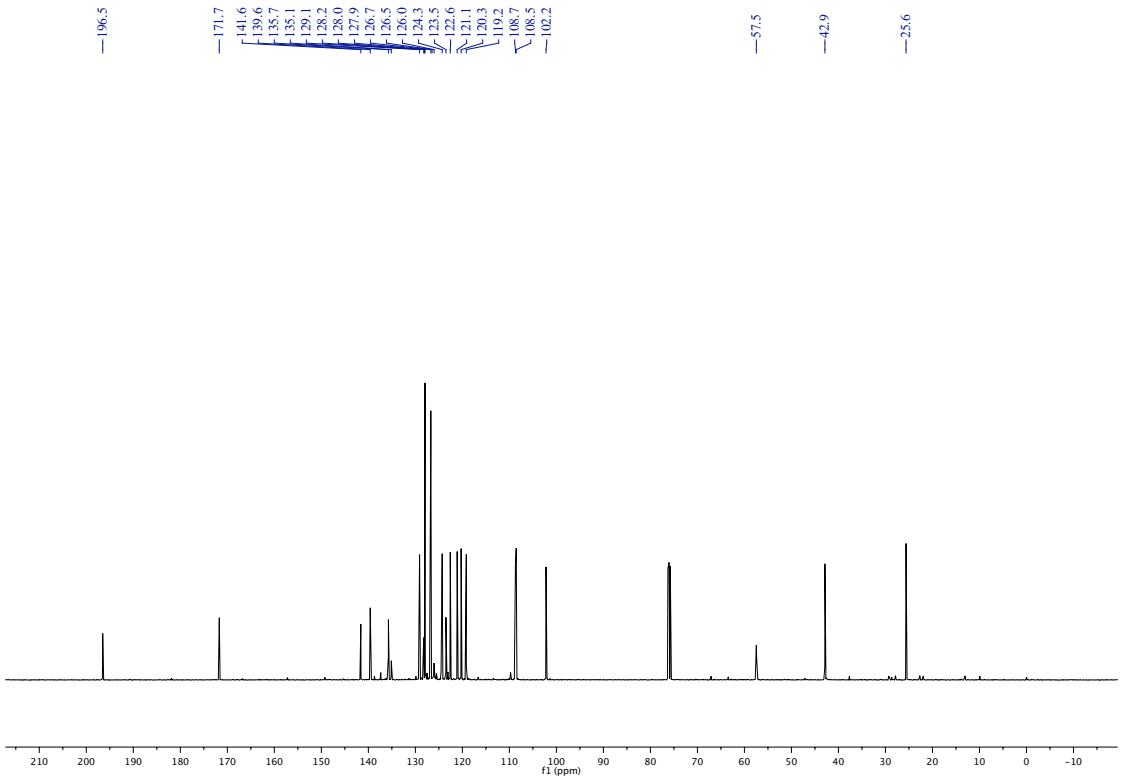

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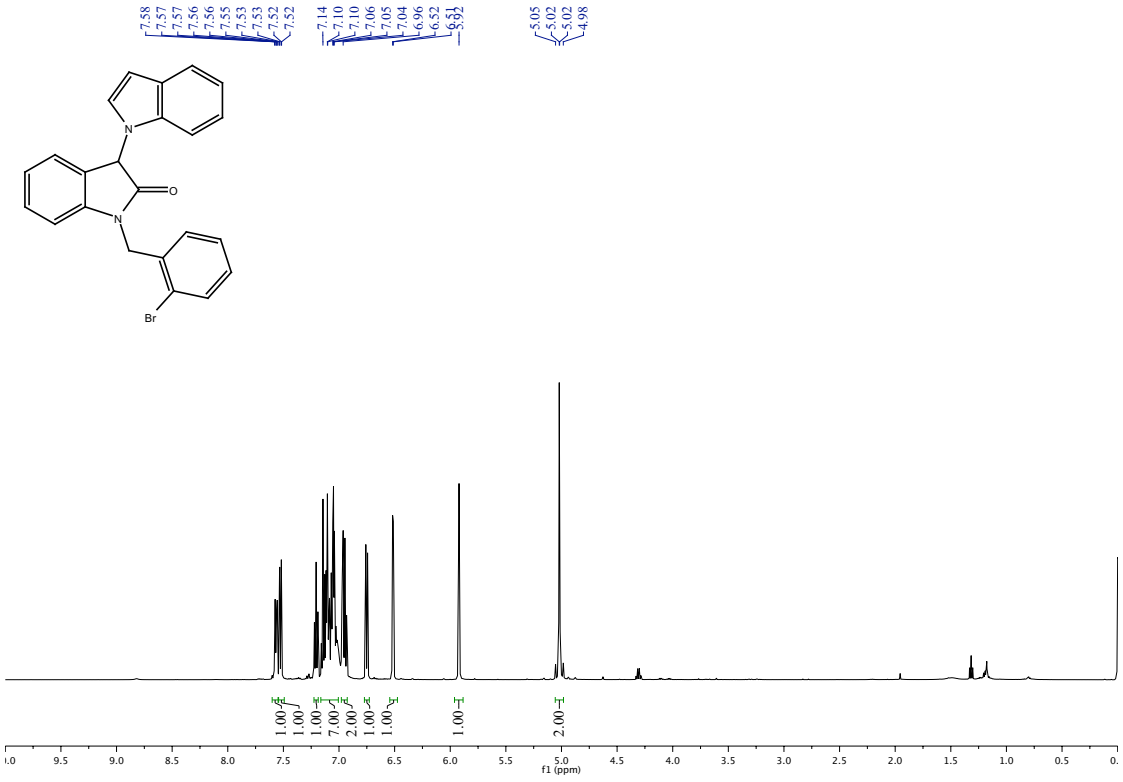

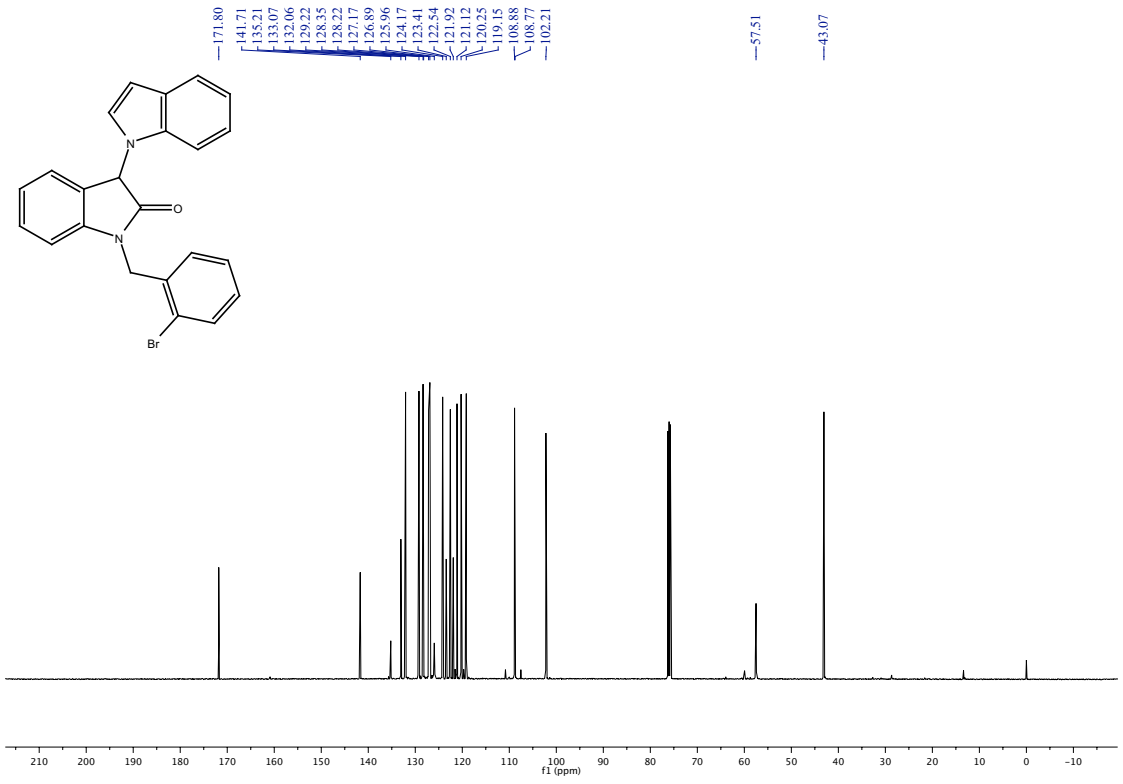

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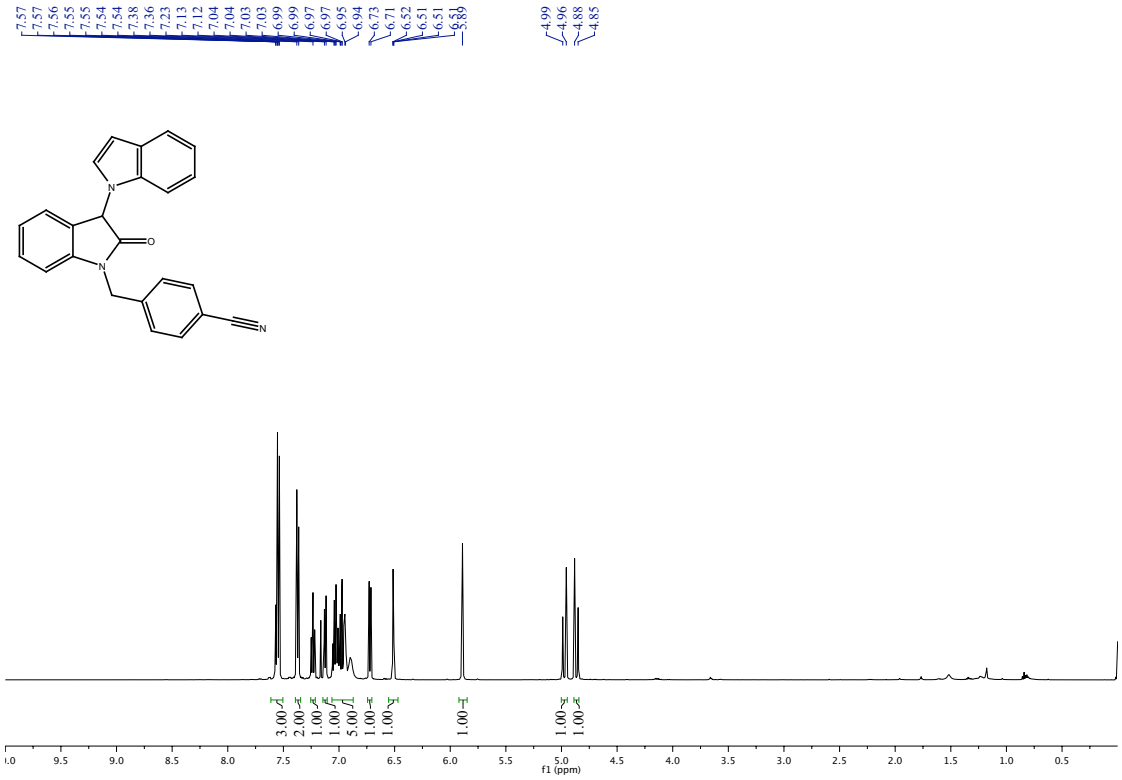
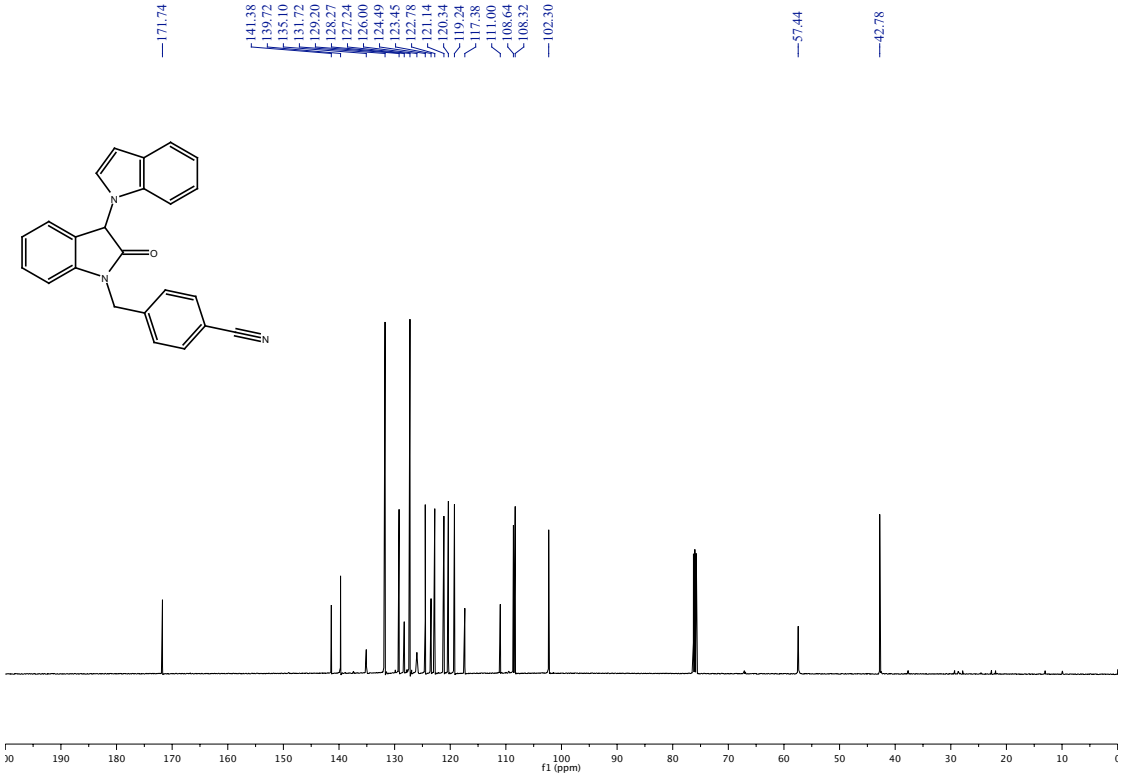
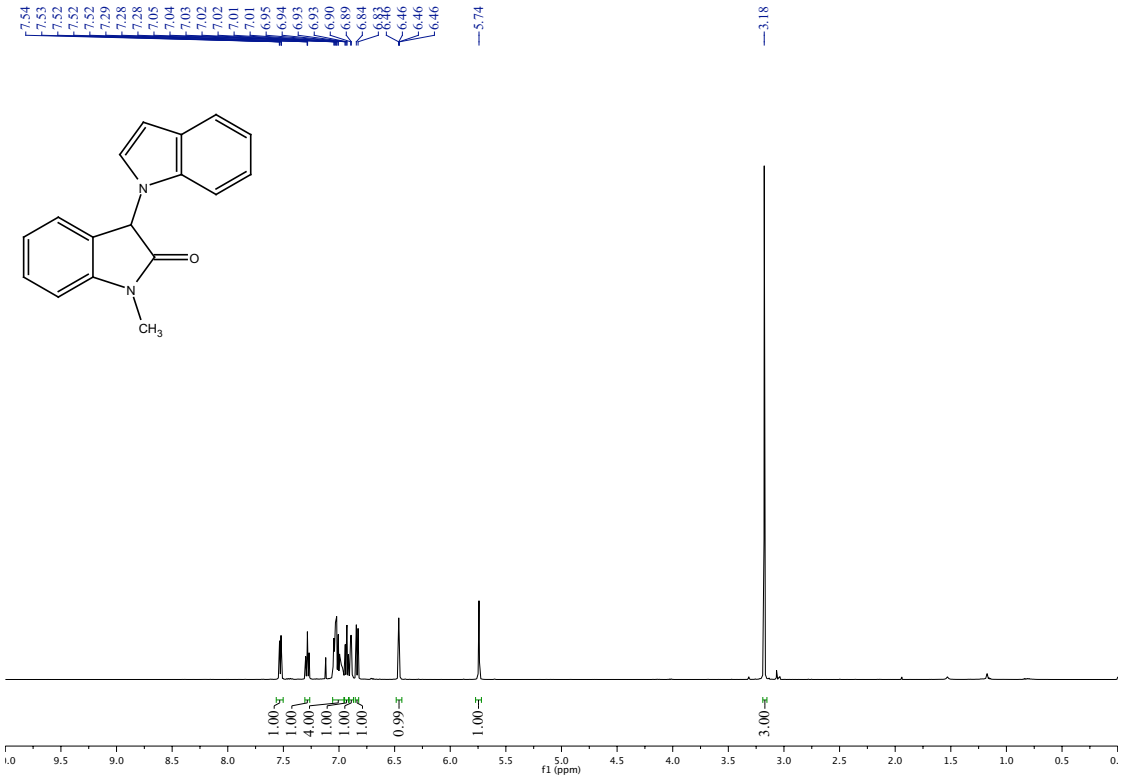
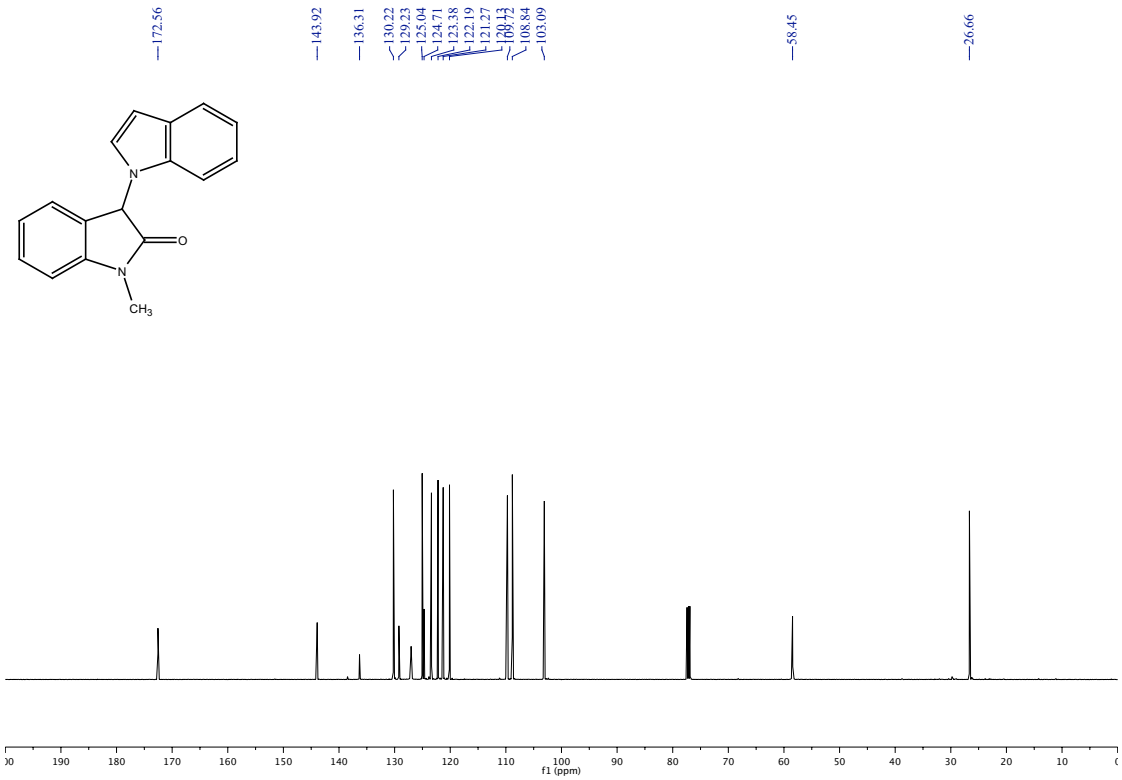




NMR Spectra for Compound 2-8a





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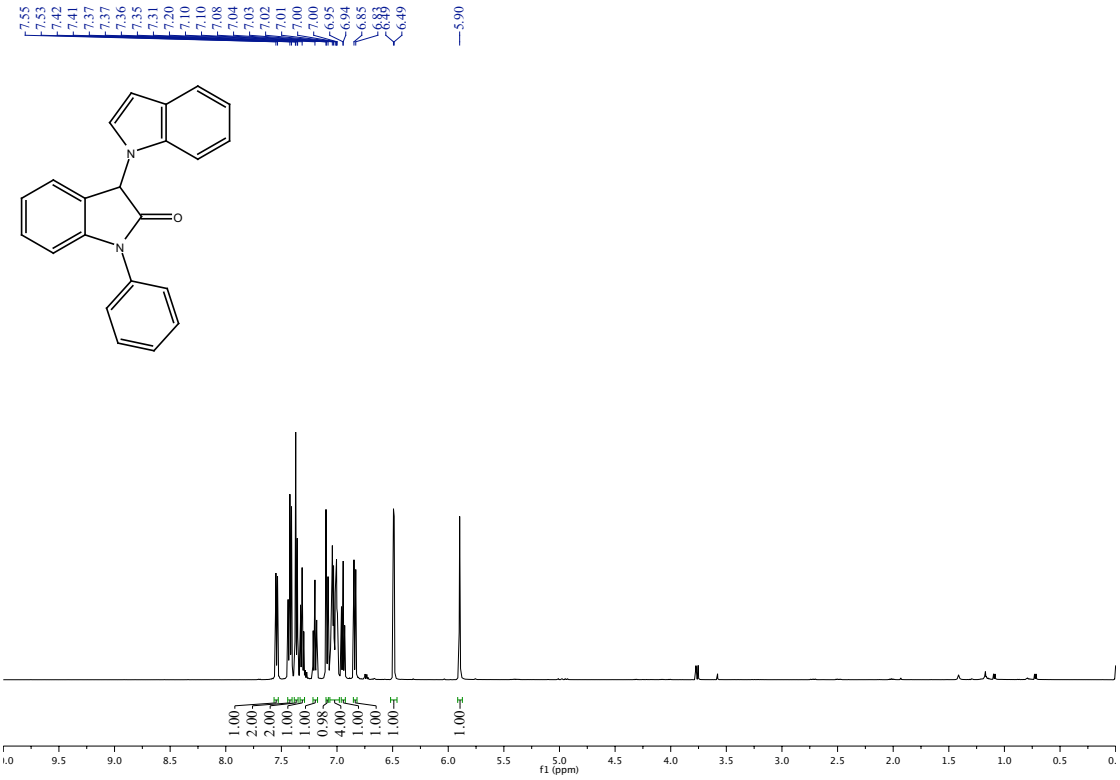

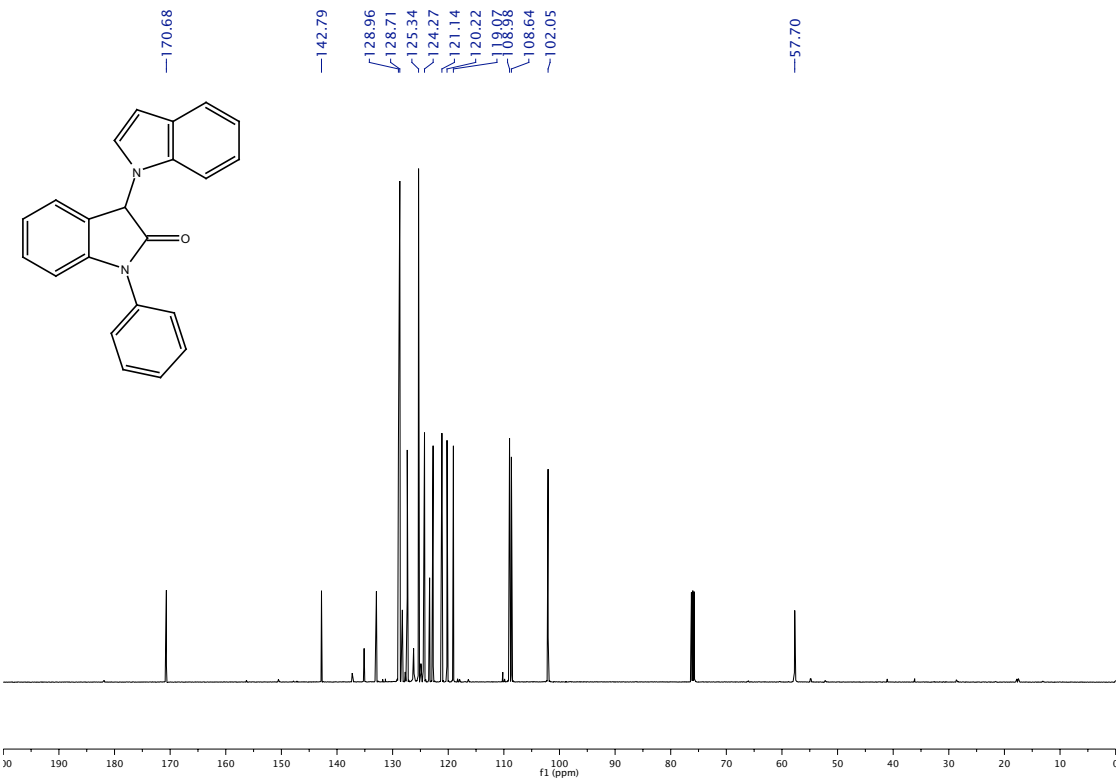

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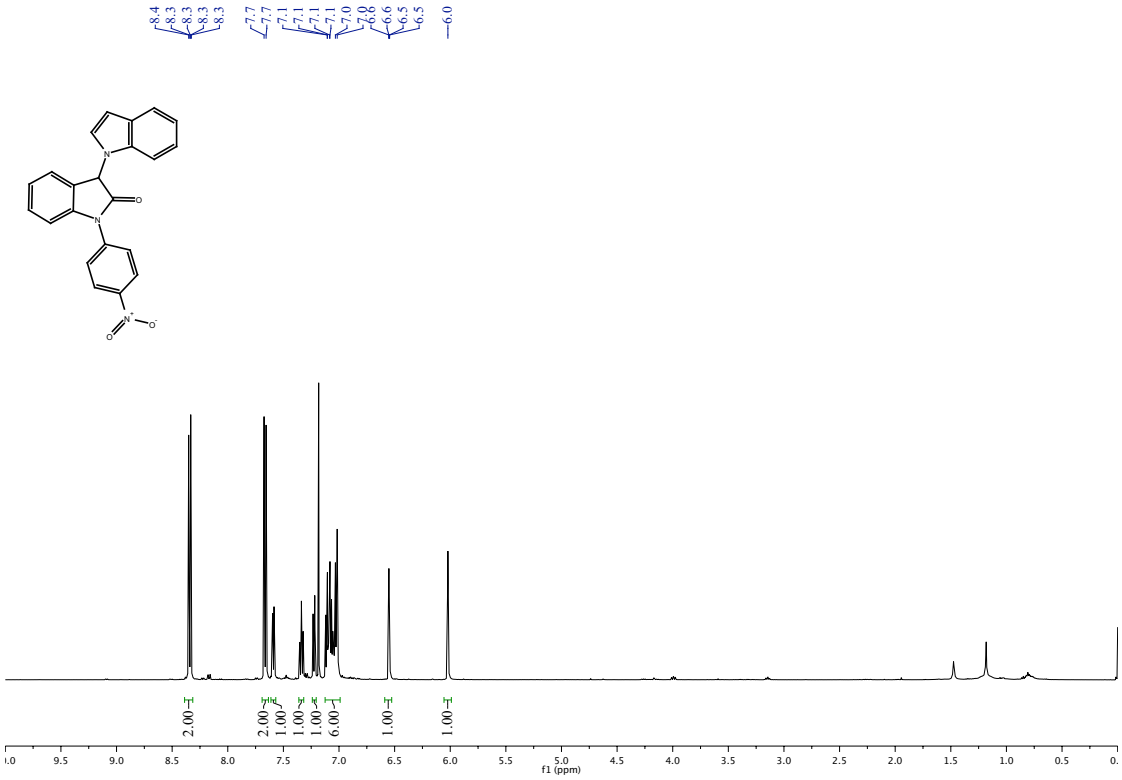

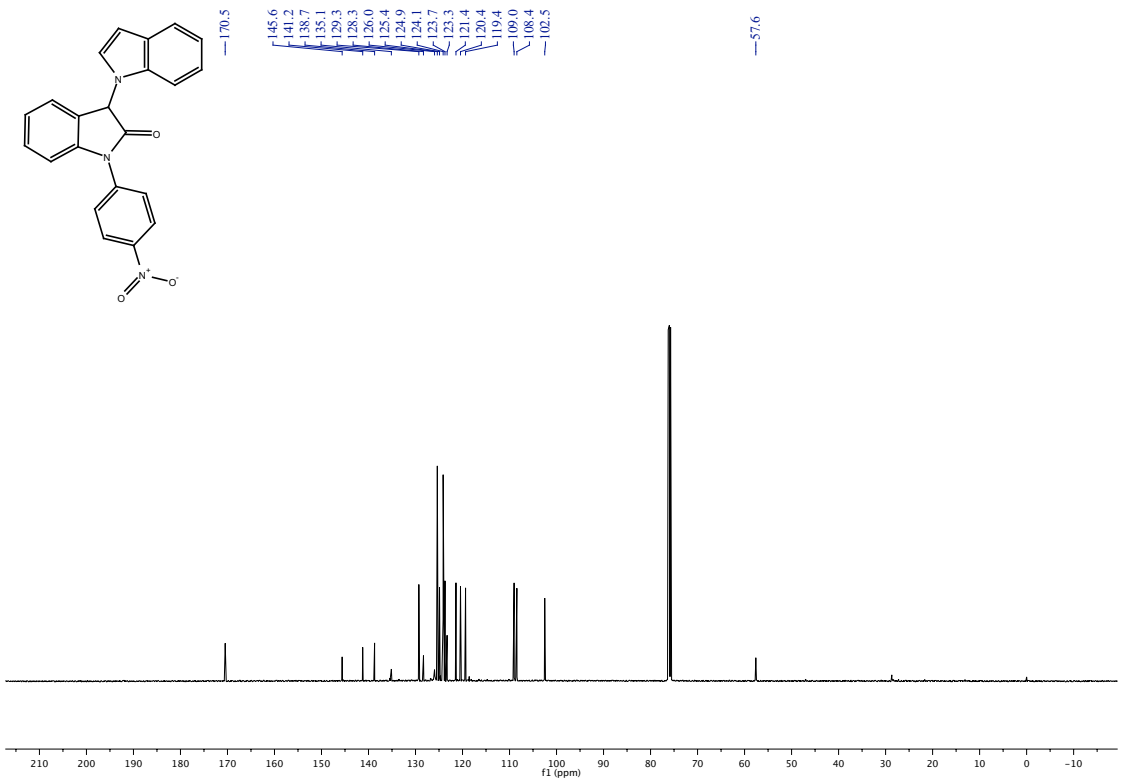

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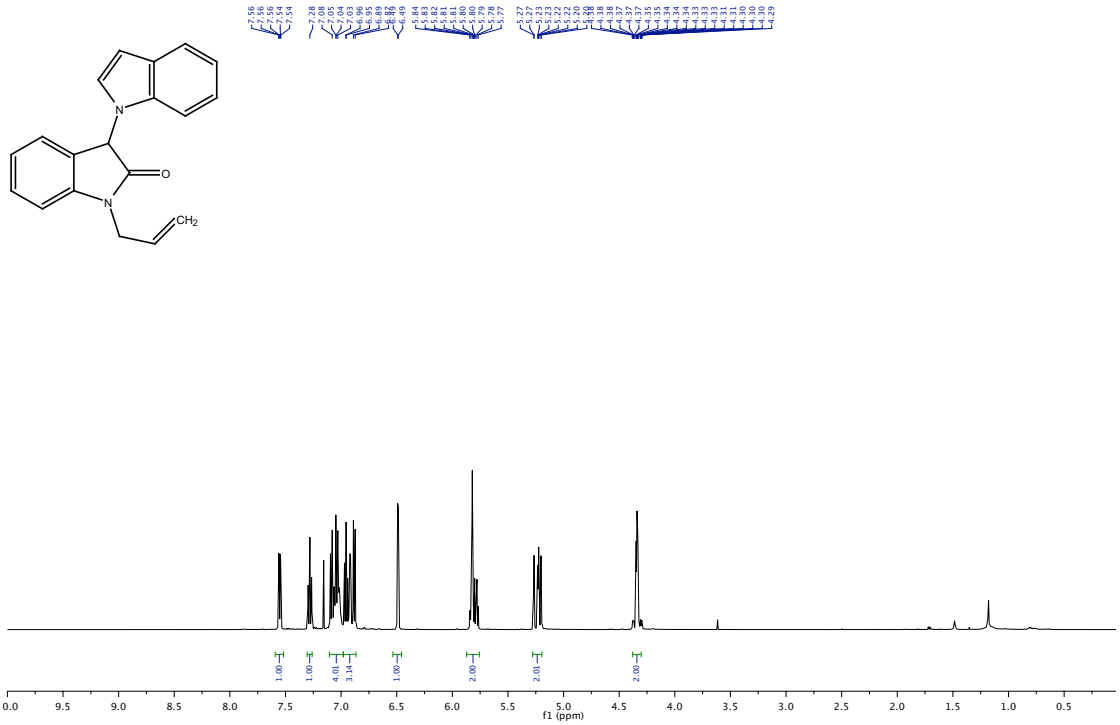

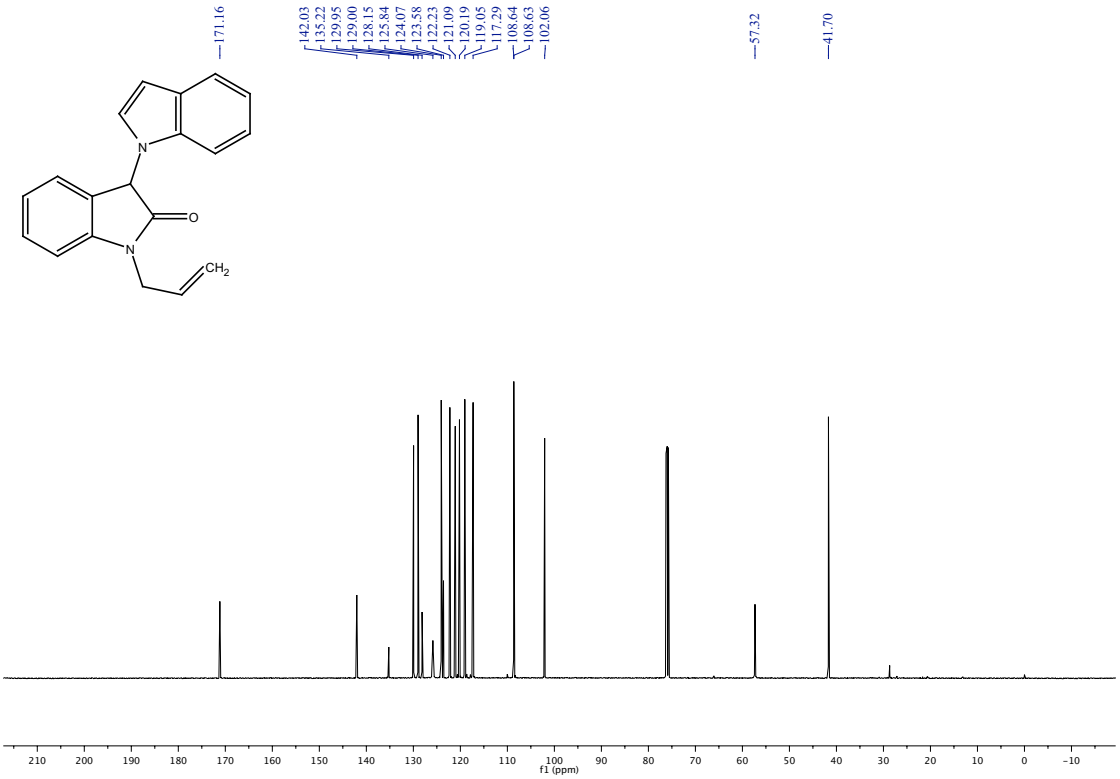

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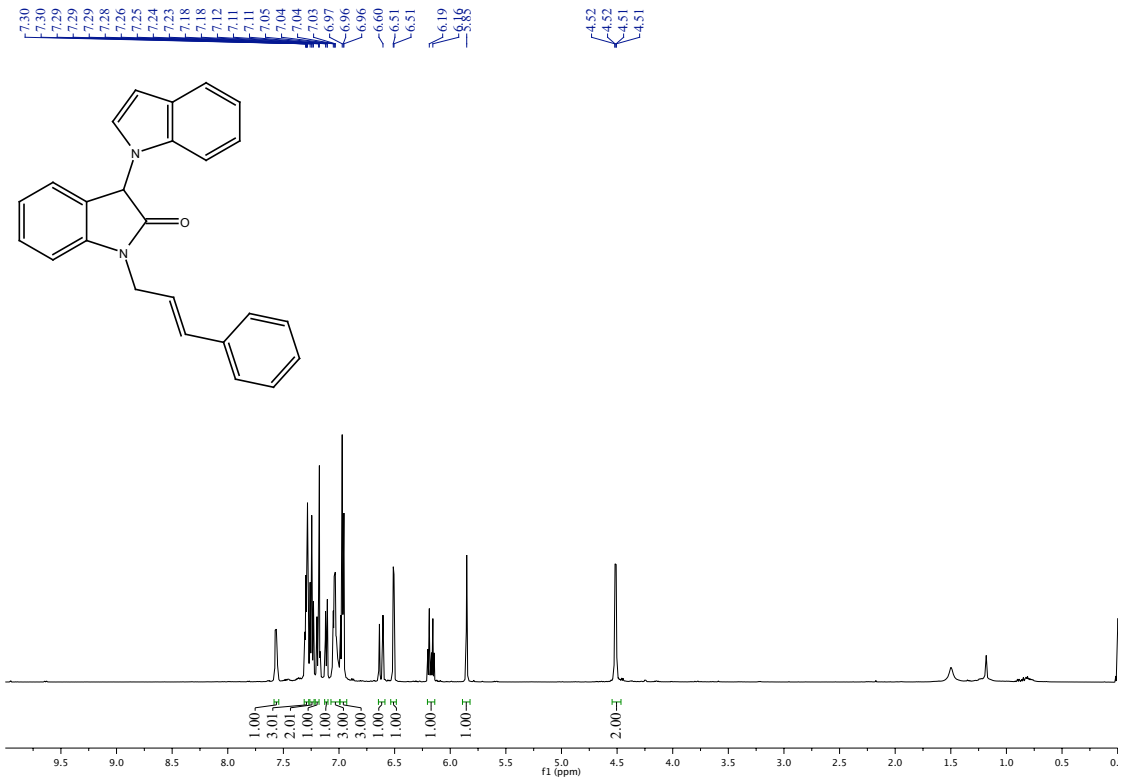

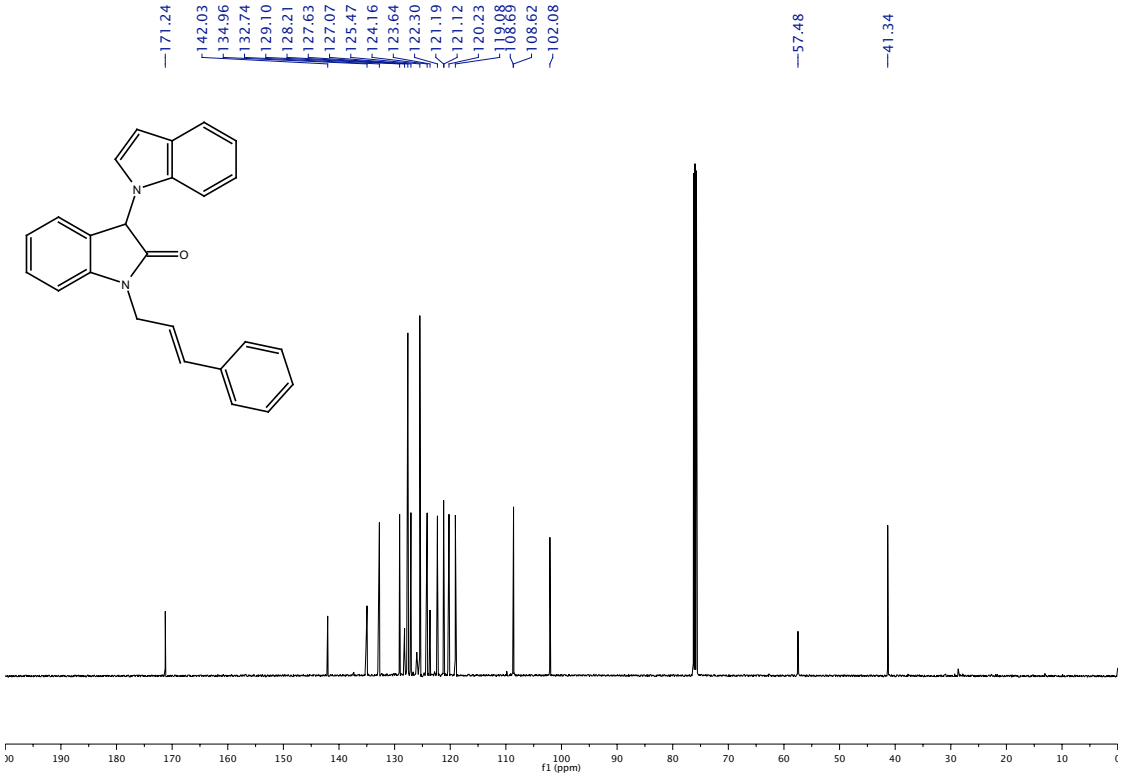

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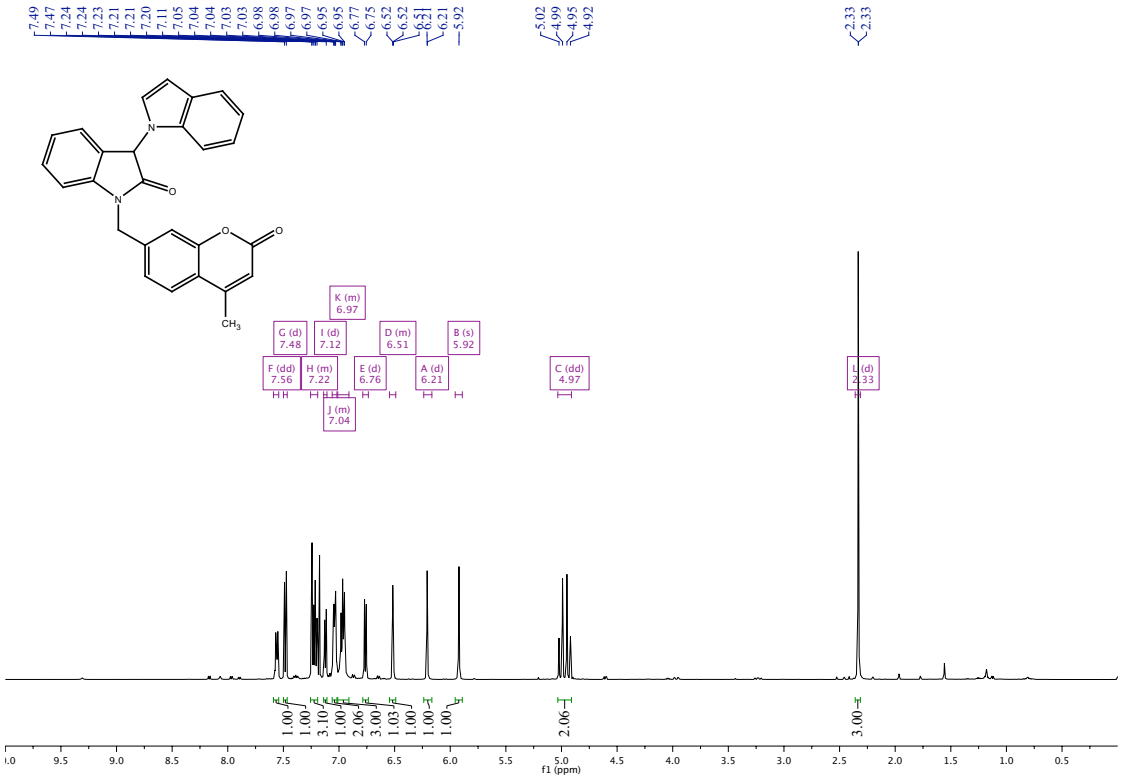
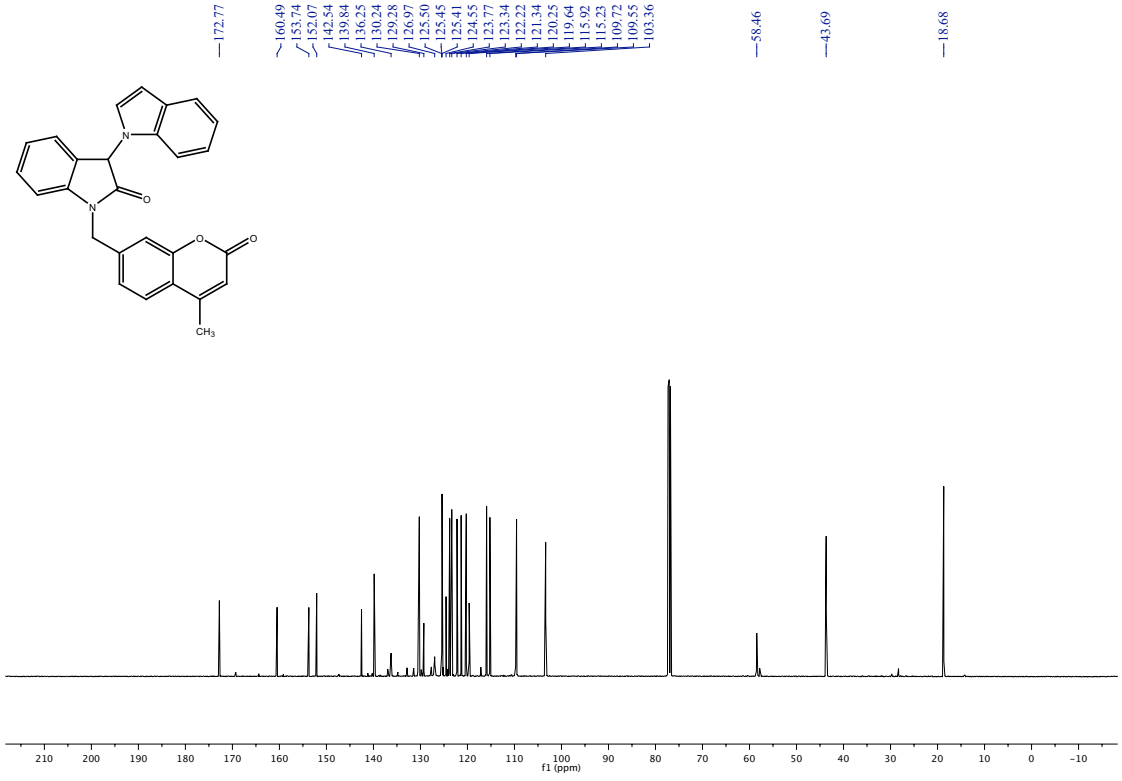
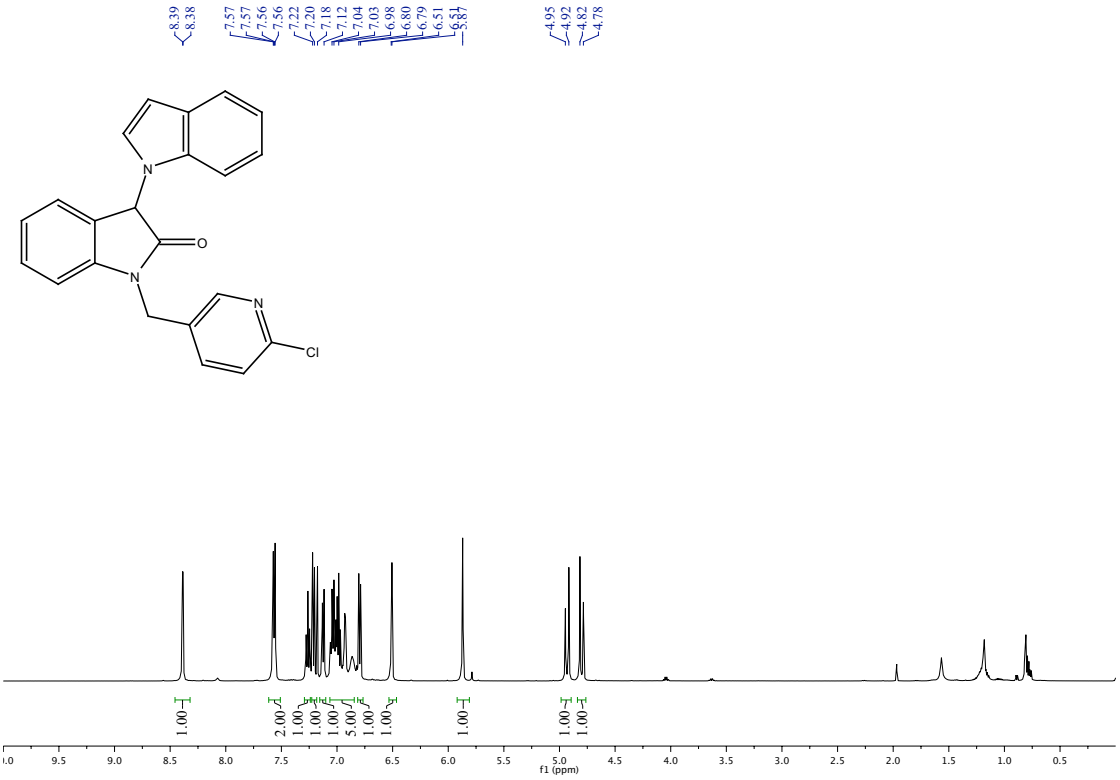
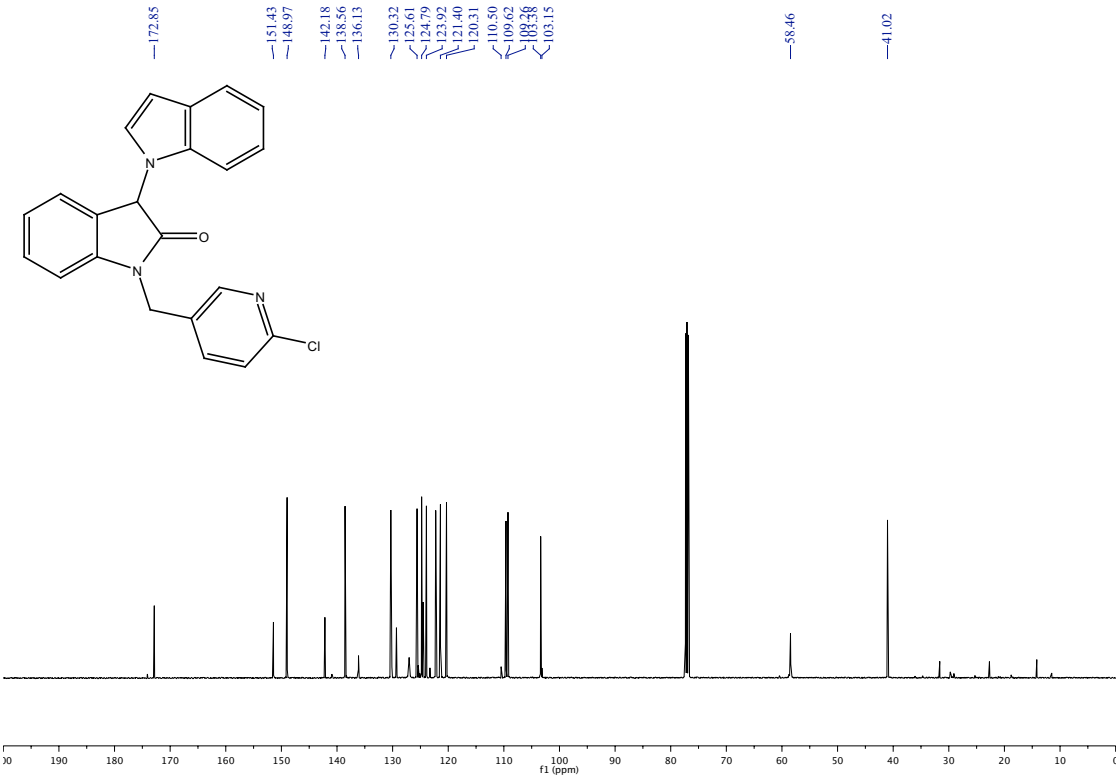




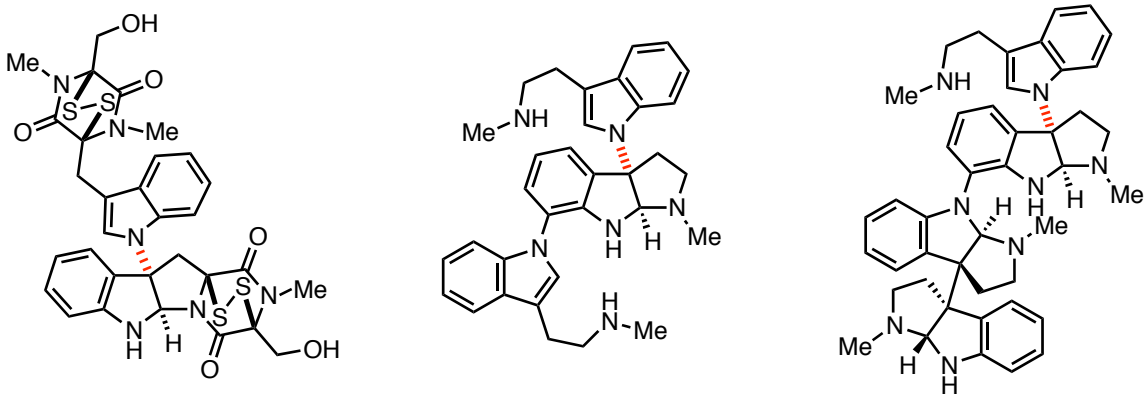
NMR Spectra for Compound 2-8g





Chapter 3-1 Natural products with N1-C3 bis-indoles linkages

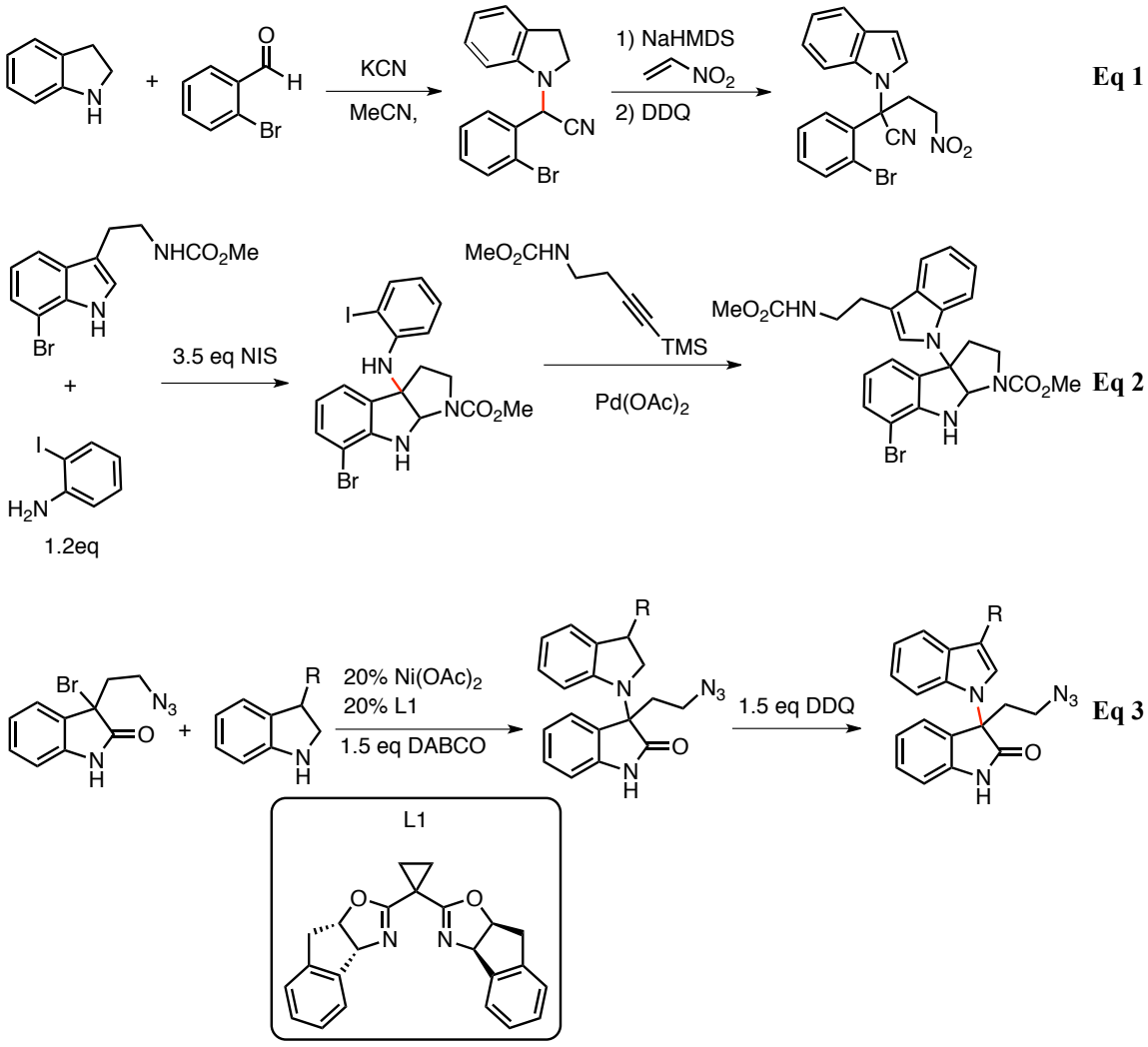
Figure 3-1.1: Naturally Occuring N1-C3 Bis-indole Linkages



Chetomine **Psychotrimine** **Psychotetramine**

It has previously been shown that redox amination can make an N1-C3 linkage between two indoles. The polyindole alkaloids chetomine,[1] psychotrimine,[2] and psychotetramine[3] are natural products all containing a unique, N1-C3 bis-indole linkage (Figure 3-1.1). Chetomine was first reported in 1966 and to date, no total syntheses of it exist. Psychotrimine and psychotetramine were first isolated in 2004 from the *psychotria rostrata*.[1] They have been the subject of total syntheses by the Baran group and the Takayama group.[2,3] Both syntheses focused on the need to make the unique N1-C3 bisindole linkage present in the respective molecules as a key step.[4] Takayama generated the N1-C3 linkage via a Strecker reaction with indoline and 2-bromobenzaldehyde (Table 3-1.1, Eq 1).

Table 3-1.1: Previous Methodologies for N1-C3 Linkage Formation



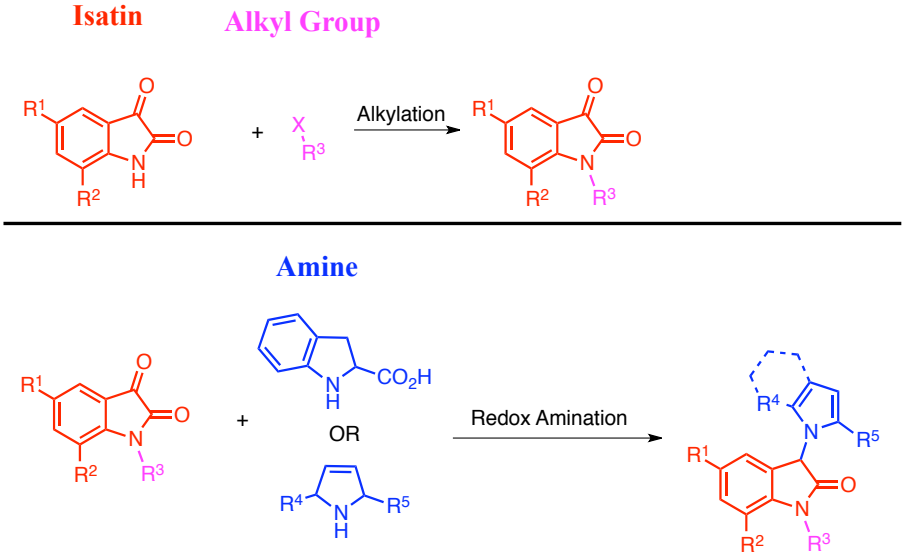
The indoline was carried on for several steps before eventually being oxidized to indole using a stoichiometric amount of oxidant. Baran used a different approach to synthesize psychotrimine.[2] He combined an iodoaniline and a protected tryptamine (Eq 2, Table 3-1.1) using three equivalents of NIS to make the desired N1-C3 bond. Then, in the next step, performed a Pd-catalyzed Larock annulation to form the indole of psychotrimine. More recently Wang used a nickel-catalyzed approach to generate N1-C3 linkages (Eq 3) as part of a formal synthesis of psychotrimine.[5] In order to make the

desired N1-C3 linkage, indolines were used which were then oxidized to indoles. Wang showed that use of indoles gave addition at the 3-position of the indole, even for 3-substituted indoles. While all of these approaches show a high degree of chemical ingenuity and synthetic creativity, they also underscore the need for simple methods to construct N1-C3 bisindole linkages. None of them could both form the carbon-nitrogen bond and produce the indole in one step. In each case a second step was needed to form the indole. In contrast, our work with redox amination of isatins with indoline 2-carboxylic acids accomplishes both of these in a single step.

Chapter 3-2 Library strategy

In order to both extend the scope of redox amination and create potentially bioactive molecules containing N1-C3 linkages, we set about generating a library of molecules via redox amination of substituted isatins and either indoline-2-carboxylic acid or pyrrolines. We envisioned that each library member would be synthesized in two steps, the first step involving alkylation of the isatin with an alkyl group, and the second step being the redox amination of the alkylated isatin with an amine-containing

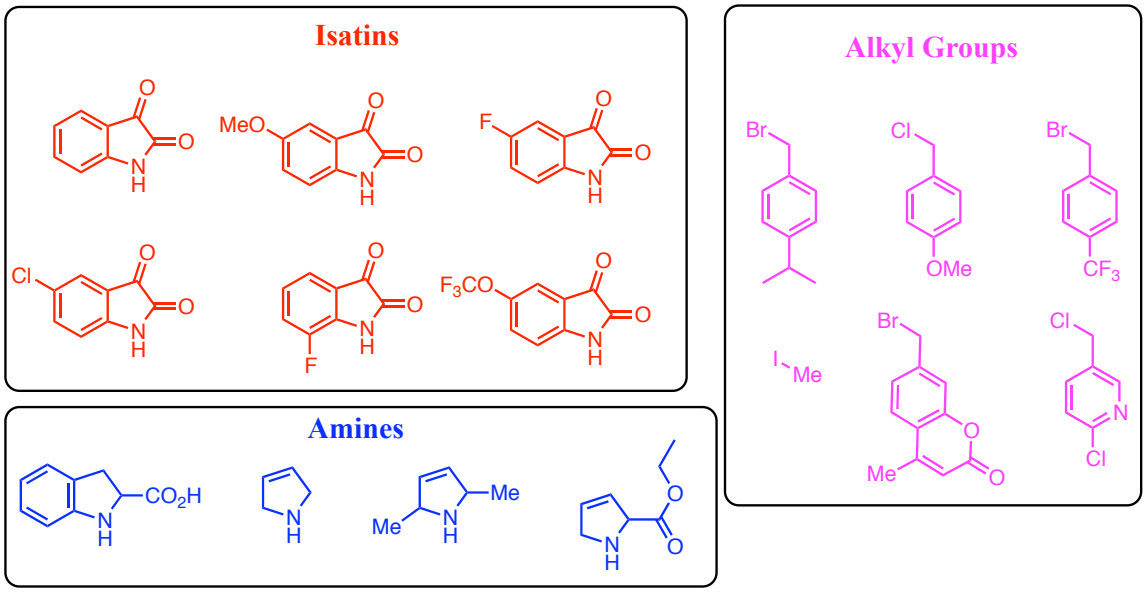
Scheme 3-2.1: Plan for library synthesis



heterocycle (Scheme 3-2.1).

To achieve diversity, we foresaw using six different alkyl group, six different isatins, and four different amines consisting of indoline-2-carboxylic acid and three pyrrolines. These groups were chosen on the basis of their molecular diversity and potential biological activities. They are shown in Figure 3-2.1.

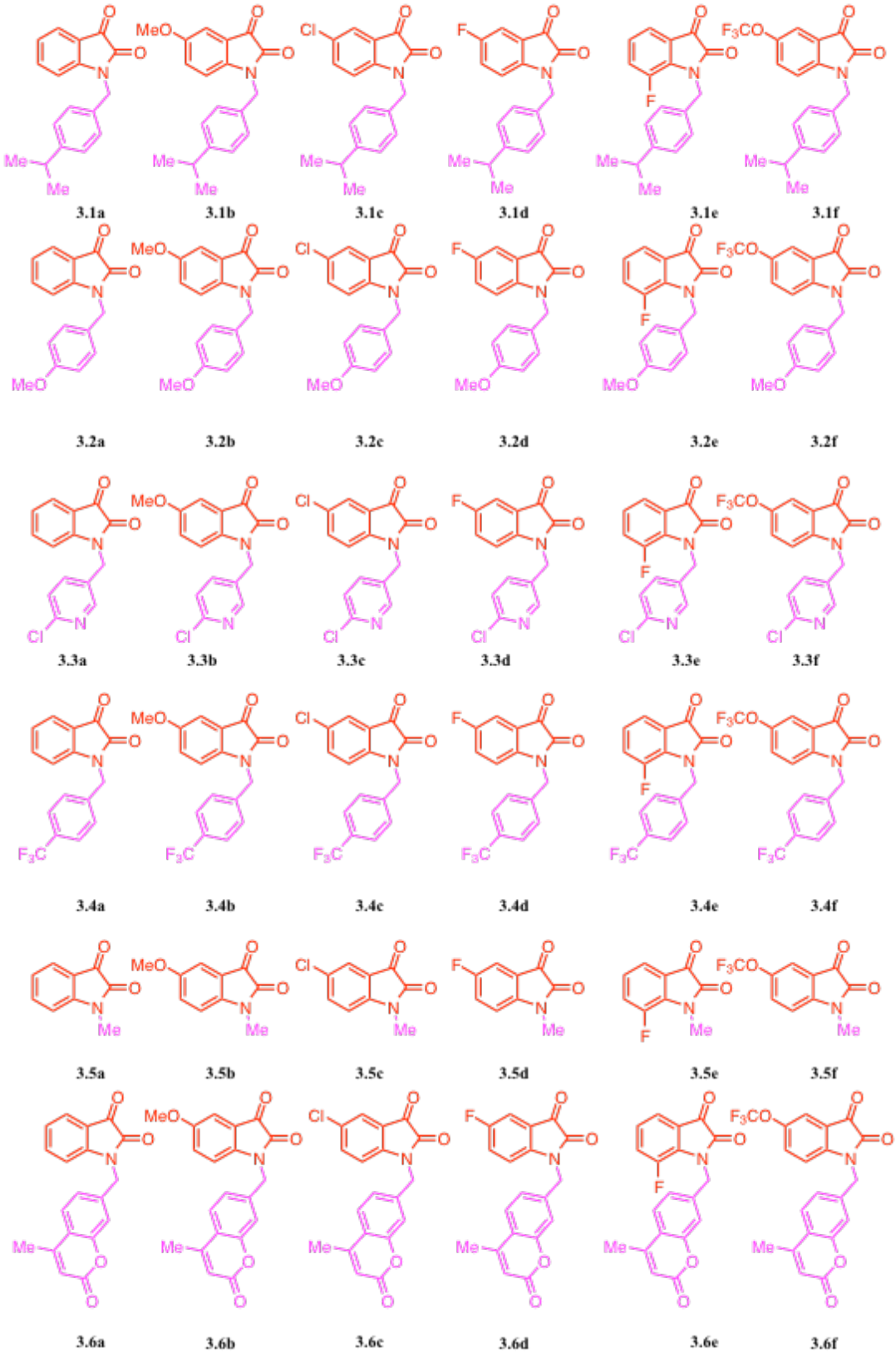
Figure 3-2.1: Groups for Library Synthesis



It was initially envisioned that all reactions would be performed on a Chemspeed Accelerator SLT-100, an automated parallel synthesis platform for the library synthesis. This necessitated optimizing both steps of the reaction for conditions compatible with the Chemspeed and universal for all reactants in the library. To accomplish this we partnered with Dr. Prashi Jain at the KU Center for Chemical Methodologies and Library Development (CMLD). After their optimization, it was found that the ideal conditions for the library synthesis were to perform the reaction in two discrete steps. The alkylation of

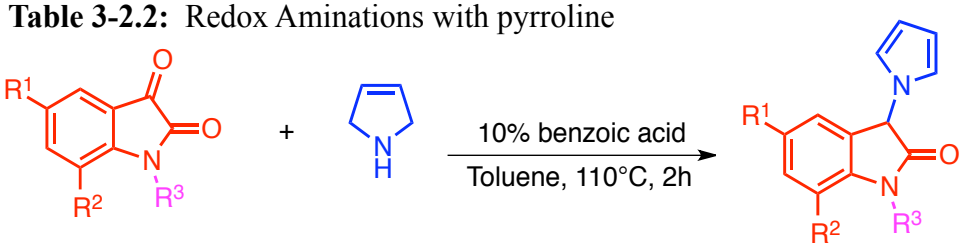
isatin was found to precede best under microwave irradiation at 160 °C. This 36-member library of starting materials was synthesized (Table 3-2.1).

Table 3-2.1: Alkyl Isatins



For the redox amination step of library synthesis, the previously optimized conditions for redox amination using pyrroline and indoline-2-carboxylic acid were utilized. All compounds and final purities are summarized (Table 3-2.2 through 3-2.5).

Table 3-2.2: Redox Aminations with pyrroline



3.1a - 3.6f **3.7** **(3.1a-1) - (3.6f-1)**

Sample ID	R^1	R^2	R^3	Fraction Purity (UV Area %)	Actual Mass	Yield (after 2 steps)
3.1a-1	H	H	4-*i*PrBn	98.9%	32.3mg	10%
3.1b-1	OMe	H	4-*i*PrBn	97.5%	17.5mg	24%
3.1c-1	Cl	H	4-*i*PrBn	93.2%	11.8mg	16%
3.1d-1	F	H	4-*i*PrBn	92.5%	24.7mg	35%
3.1e-1	H	F	4-*i*PrBn	94.6%	27.5mg	40%
3.1f-1	OCF_3	H	4-*i*PrBn	97.3%	97.3mg	23%
3.2a-1	H	H	4-OMeBn	97.9%	28.0mg	44%
3.2b-1	OMe	H	4-OMeBn	94.5%	9.8mg	14%
3.2c-1	F	H	4-OMeBn	98.8%	21.1mg	31%
3.2d-1	H	F	4-OMeBn	96.7%	16.2mg	24%
3.2e-1	Cl	H	4-OMeBn	93.2%	18.4mg	26%
3.2f-1	OCF_3	H	4-OMeBn	35.3%	3.7mg	N/A
3.3a-1	H	H	6-ClPyridin-3-yl	91.1%	5.9mg	9%
3.3b-1	OMe	H	6-ClPyridin-3-yl	94.4%	24.0mg	34%
3.3c-1	H	F	6-ClPyridin-3-yl	13.6%	90.0mg	N/A
3.3d-1	F	H	6-ClPyridin-3-yl	4.0%	7.7mg	N/A
3.3e-1	OCF_3	H	6-ClPyridin-3-yl	0.0%	86.3mg	N/A
3.3f-1	Cl	H	6-ClPyridin-3-yl	12.5%	4.2mg	N/A

3.4a-1	H	H	4-CF_3Bn	100.0%	55.6mg	16%
3.4b-1	OMe	H	4-CF_3Bn	90.7%	4.9mg	6%
3.4c-1	F	H	4-CF_3Bn	0.3%	10.4mg	N/A
3.4d-1	H	F	4-CF_3Ph	12.7%	99.1mg	N/A
3.4e-1	OCF_3	H	4-CF_3Bn	0.0%	3.1mg	N/A
3.4f-1	Cl	H	4-CF_3Bn	0.0%	0.0mg	N/A
3.5a-1	H	H	Me	70.6%	18.5mg	N/A
3.5b-1	OMe	H	Me	85.0%	16.0mg	N/A
3.5c-1	F	H	Me	55.8%	15.8mg	N/A
3.5d-1	H	F	Me	79.9%	14.5mg	N/A
3.5e-1	OCF_3	H	Me	24.4%	15.3mg	N/A
3.5f-1	Cl	H	Me	52.3%	17.3mg	N/A
3.6a-1	H	H	4-methyl-2-oxo-2*H*-chromen-7-yl	36.5%	6.4mg	N/A
3.6b-1	OMe	H	4-methyl-2-oxo-2*H*-chromen-7-yl	1.8%	0.7mg	N/A
3.6c-1	F	H	4-methyl-2-oxo-2*H*-chromen-7-yl	2.8%	98.0mg	N/A
3.6d-1	H	F	4-methyl-2-oxo-2*H*-chromen-7-yl	5.5%	8.0mg	N/A
3.6e-1	OCF_3	H	4-methyl-2-oxo-2*H*-chromen-7-yl	67.8%	14.7mg	N/A
3.6f-1	Cl	H	4-methyl-2-oxo-2*H*-chromen-7-yl	73.4%	15.4mg	N/A

Purity of Pyrrole Oxindoles

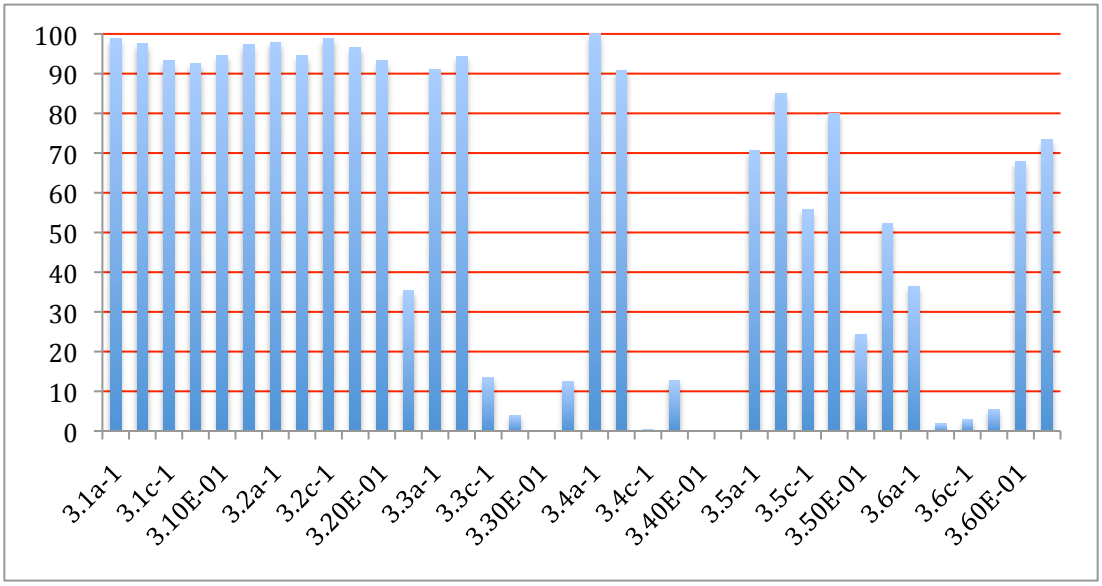
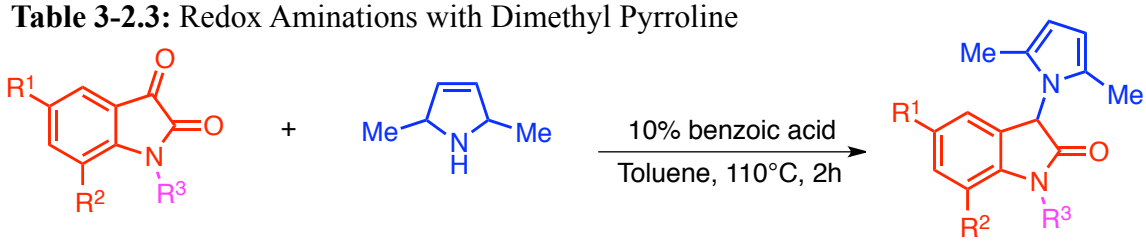


Table 3-2.3: Redox Aminations with Dimethyl Pyrroline



3.1a - 3.6f **3.8** **(3.1a-2) - (3.6f-2)**

Sample ID	R^1	R^2	R^3	Purity (UV Area %)	Actual Mass (mg)	Yield (%)
3.1a-2	H	H	4-*i*PrBn	100.0%	16.0mg	15%
3.1b-2	OMe	H	4-*i*PrBn	100.0%	10.0 mg	9%
3.1c-2	Cl	H	4-*i*PrBn	100.0%	32.4 mg	28%
3.1d-2	F	H	4-*i*PrBn	100.0%	38.5 mg	34%
3.1e-2	H	F	4-*i*PrBn	98.9%	15.8 mg	14%
3.1f-2	OCF_3	H	4-*i*PrBn	93.2%	6.3 mg	5%
3.2a-2	H	H	4-OMeBn	100.0%	55.3 mg	53%
3.2b-2	OMe	H	4-OMeBn	100.0%	35.5 mg	31%
3.2c-2	Cl	H	4-OMeBn	100.0%	33.7 mg	30%
3.2d-2	F	H	4-OMeBn	95.9%	48.6 mg	45%
3.2e-2	H	F	4-OMeBn	100.0%	38.2 mg	35%

Sample ID	R^1	R^2	R^3	Purity (UV Area %)	Actual Mass (mg)	Yield (%)
3.2f-2	OCF_3	H	4-OMeBn	97.4%	22.0 mg	17%
3.3a-2	H	H	6-ClPyridin-3-yl	100.0%	37.7 mg	36%
3.3b-2	OMe	H	6-ClPyridin-3-yl	100.0%	17.7 mg	15%
3.3c-2	Cl	H	6-ClPyridin-3-yl	98.0%	12.9 mg	11%
3.3d-2	F	H	6-ClPyridin-3-yl	81.2%	19.3 mg	17%
3.3e-2	H	F	6-ClPyridin-3-yl	100.0%	14.8 mg	13%
3.3f-2	OCF_3	H	6-ClPyridin-3-yl	83.3%	19.8 mg	15%
3.4a-2	H	H	4-CF_3Bn	100.0%	28.7 mg	25%
3.4b-2	OMe	H	4-CF_3Bn	96.8%	23.5 mg	19%
3.4c-2	Cl	H	4-CF_3Bn	100.0%	14.6 mg	12%
3.4d-2	F	H	4-CF_3Bn	94.0%	12.8 mg	11%
3.4e-2	H	F	4-CF_3Bn	98.7%	36.7 mg	30%
3.4f-2	OCF_3	H	4-CF_3Bn	92.8%	18.9 mg	13%
3.5a-2	H	H	Me	98.1%	26.5 mg	37%
3.5b-2	OMe	H	Me	98.3%	40.2 mg	50%
3.5c-2	Cl	H	Me	98.0%	24.2 mg	29%
3.5d-2	F	H	Me	96.9%	25.0 mg	32%
3.5e-2	H	F	Me	99.1%	21.7 mg	28%
3.5f-2	OCF_3	H	Me	97.8%	19.1 mg	20%
3.6a-2	H	H	4-methyl-2-oxo-2*H*-chromen-7-yl	98.6%	14.4 mg	12%
3.6b-2	OMe	H	4-methyl-2-oxo-2*H*-chromen-7-yl	90.2%	27.0 mg	21%
3.6c-2	Cl	H	4-methyl-2-oxo-2*H*-chromen-7-yl	100.0%	22.8 mg	18%
3.6d-2	F	H	4-methyl-2-oxo-2*H*-chromen-7-yl	98.0%	17.9 mg	14%
3.6e-2	H	F	4-methyl-2-oxo-2*H*-chromen-7-yl	100.0%	25.9 mg	21%
3.6f-2	OCF_3	H	4-methyl-2-oxo-2*H*-chromen-7-yl	97.4%	29.8 mg	21%

Purity of Dimethyl Oxindoles

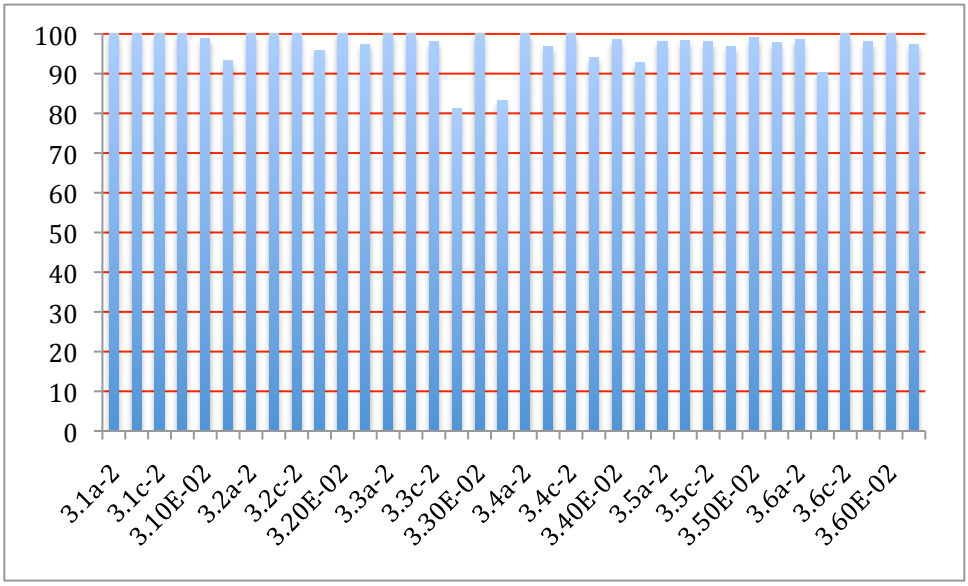
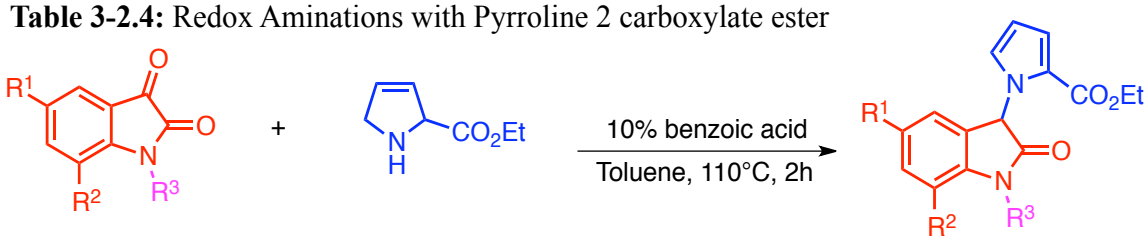


Table 3-2.4: Redox Aminations with Pyrroline 2 carboxylate ester



3.1a - 3.6f **3.9** **(3.1a-3) - (3.6f-3)**

Sample ID	R^1	R^2	R^3	Purity (UV Area %)	Actual Mass	Yield (%)
3.1a-3	H	H	4-*i*PrBn	100.00%	50.3 mg	42%
3.1b-3	OMe	H	4-*i*PrBn	100.00%	48.9 mg	38%
3.1c-3	Cl	H	4-*i*PrBn	100.00%	44.2 mg	34%
3.1d-3	F	H	4-*i*PrBn	100.00%	46.8 mg	37%
3.1e-3	H	F	4-*i*PrBn	100.00%	62.8 mg	50%
3.1f-3	OCF_3	H	4-*i*PrBn	100.00%	65.0 mg	45%
3.2a-3	H	H	4-OMeBn	100.00%	54.4 mg	46%
3.2b-3	OMe	H	4-OMeBn	98.13%	71.0 mg	56%
3.2c-3	Cl	H	4-OMeBn	97.96%	48.5 mg	38%
3.2d-3	F	H	4-OMeBn	97.94%	54.5 mg	45%

3.2e-3	H	F	4-OMeBn	100.00%	49.9 mg	41%
3.2f-3	OCF_3	H	4-OMeBn	100.00%	39.3 mg	28%
3.3a-3	H	H	6-ClPyridin-3-yl	100.00%	57.9 mg	49%
3.3b-3	OMe	H	6-ClPyridin-3-yl	97.66%	59.8 mg	47%
3.3c-3	Cl	H	6-ClPyridin-3-yl	98.35%	48.2 mg	37%
3.3d-3	F	H	6-ClPyridin-3-yl	94.59%	50.5 mg	41%
3.3e-3	H	F	6-ClPyridin-3-yl	98.33%	50.6 mg	41%
3.3f-3	OCF_3	H	6-ClPyridin-3-yl	98.65%	57.7 mg	4%
3.4a-3	H	H	4-CF_3Bn	100.00%	64.6 mg	50%
3.4b-3	OMe	H	4-CF_3Bn	95.97%	17.6 mg	13%
3.4c-3	Cl	H	4-CF_3Bn	100.00%	52.0 mg	37%
3.4d-3	F	H	4-CF_3Bn	100.00%	37.7 mg	28%
3.4e-3	H	F	4-CF_3Bn	100.00%	53.9 mg	40%
3.4f-3	OCF_3	H	4-CF_3Bn	100.00%	61.6 mg	40%
3.5a-3	H	H	Me	92.03%	43.4 mg	51%
3.5b-3	OMe	H	Me	96.85%	38.4 mg	41%
3.5c-3	Cl	H	Me	99.01%	47.3 mg	50%
3.5d-3	F	H	Me	100.00%	37.1 mg	41%
3.5e-3	H	F	Me	100.00%	49.6 mg	55%
3.5f-3	OCF_3	H	Me	97.99%	51.9 mg	47%
3.6a-3	H	H	4-methyl-2-oxo-2*H*-chromen-7-yl	90.58%	16.3 mg	12%
3.6b-3	OMe	H	4-methyl-2-oxo-2*H*-chromen-7-yl	97.85%	64.8 mg	46%
3.6c-3	Cl	H	4-methyl-2-oxo-2*H*-chromen-7-yl	94.09%	44.9 mg	31%
3.6d-3	F	H	4-methyl-2-oxo-2*H*-chromen-7-yl	98.92%	38.1 mg	28%
3.6e-3	H	F	4-methyl-2-oxo-2*H*-chromen-7-yl	97.24%	67.4 mg	49%
3.6f-3	OCF_3	H	4-methyl-2-oxo-2*H*-chromen-7-yl	77.47%	45.5 mg	0%

Purity of Pyrrole Ethyl Ester Oxindoles

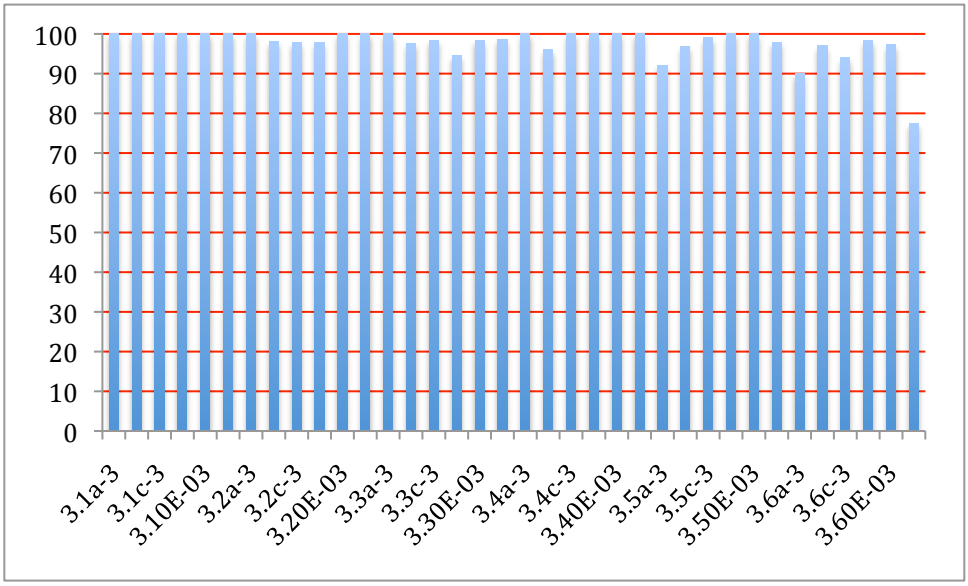
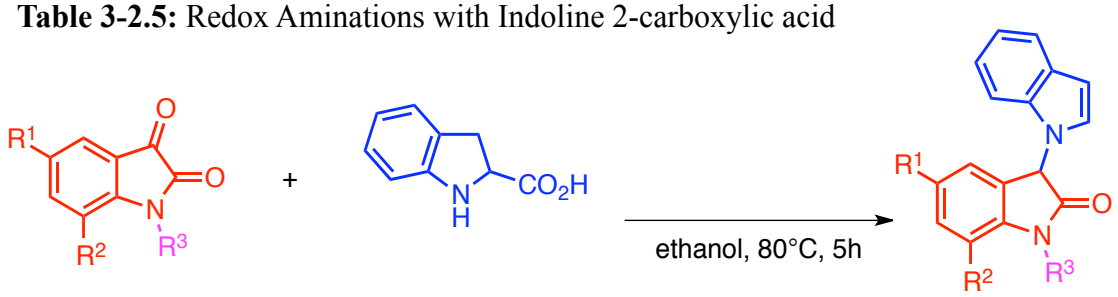


Table 3-2.5: Redox Aminations with Indoline 2-carboxylic acid



3.1a - 3.6f **3.9** **(3.1a-4) - (3.6f-4)**

Sample ID	R^1	R^2	R^3	Fraction Purity (UV Area Percent)	Actual Mass	Yield (%)
3.1a-4	H	H	4-*i*PrBn	99.7%	30.5 mg	27%
3.1b-4	OMe	H	4-*i*PrBn	99.2%	39.2 mg	32%
3.1c-4	Cl	H	4-*i*PrBn	98.6%	43.3 mg	35%
3.1d-4	F	H	4-*i*PrBn	99.5%	32.3 mg	27%
3.1e-4	H	F	4-*i*PrBn	97.4%	29.6 mg	25%
3.1f-4	OCF_3	H	4-*i*PrBn	97.7%	44.5 mg	32%
3.2a-4	H	H	4-OMeBn	96.2%	38.8 mg	35%

3.2b-4	OMe	H	4-OMeBn	97.3%	39.4 mg	33%
3.2c-4	Cl	H	4-OMeBn	91.4%	66.1 mg	55%
3.2d-4	F	H	4-OMeBn	96.4%	37.7 mg	33%
3.2e-4	H	F	4-OMeBn	95.5%	32.7 mg	28%
3.2f-4	OCF_3	H	4-OMeBn	97.0%	21.7 mg	16%
3.3a-4	H	H	6-ClPyridin-3-yl	97.2%	31.4 mg	28%
3.3b-4	OMe	H	6-ClPyridin-3-yl	92.7%	29.8 mg	25%
3.3c-4	Cl	H	6-ClPyridin-3-yl	98.2%	24.0 mg	20%
3.3d-4	F	H	6-ClPyridin-3-yl	93.7%	31.9 mg	27%
3.3e-4	H	F	6-ClPyridin-3-yl	94.5%	18.6 mg	16%
3.3f-4	OCF_3	H	6-ClPyridin-3-yl	92.7%	17.0 mg	12%
3.4a-4	H	H	4-CF_3Bn	93.4%	21.8 mg	18%
3.4b-4	OMe	H	4-CF_3Bn	93.8%	23.6 mg	18%
3.4c-4	Cl	H	4-CF_3Bn	95.6%	27.1 mg	20%
3.4d-4	F	H	4-CF_3Bn	90.0%	25.7 mg	20%
3.4e-4	H	F	4-CF_3Bn	96.0%	28.1 mg	22%
3.4f-4	OCF_3	H	4-CF_3Bn	97.4%	29.5 mg	20%
3.5a-4	H	H	Me	97.9%	36.5 mg	46%
3.5b-4	OMe	H	Me	97.8%	37.9 mg	43%
3.5c-4	Cl	H	Me	94.9%	34.3 mg	39%
3.5d-4	F	H	Me	94.6%	35.0 mg	42%
3.5e-4	H	F	Me	97.4%	35.6 mg	42%
3.5f-4	OCF_3	H	Me	96.8%	37.7 mg	36%
3.6a-4	H	H	4-methyl-2-oxo-2*H*-chromen-7-yl	77.6%	7.4 mg	15%
3.6b-4	OMe	H	4-methyl-2-oxo-2*H*-chromen-7-yl	100.0%	21.0 mg	16%
3.6c-4	Cl	H	4-methyl-2-oxo-2*H*-chromen-7-yl	91.6%	92.9 mg	68%
3.6d-4	F	H	4-methyl-2-oxo-2*H*-chromen-7-yl	97.2%	12.6 mg	10%
3.6e-4	H	F	4-methyl-2-oxo-2*H*-chromen-7-yl	88.5%	61.1 mg	47%
3.6f-4	OCF_3	H	4-methyl-2-oxo-2*H*-chromen-7-yl	82.0%	20.8 mg	27%

Purity of Indole Oxindoles

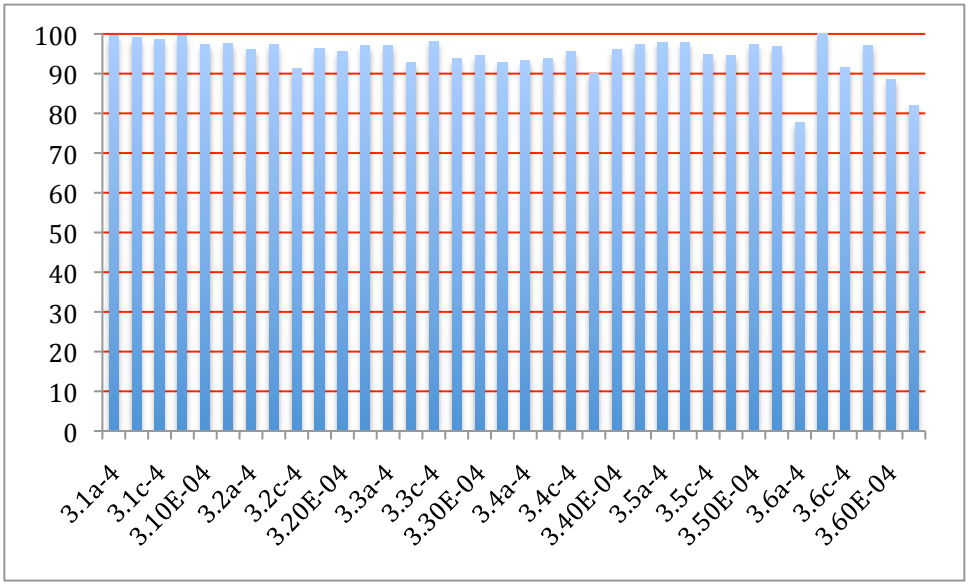
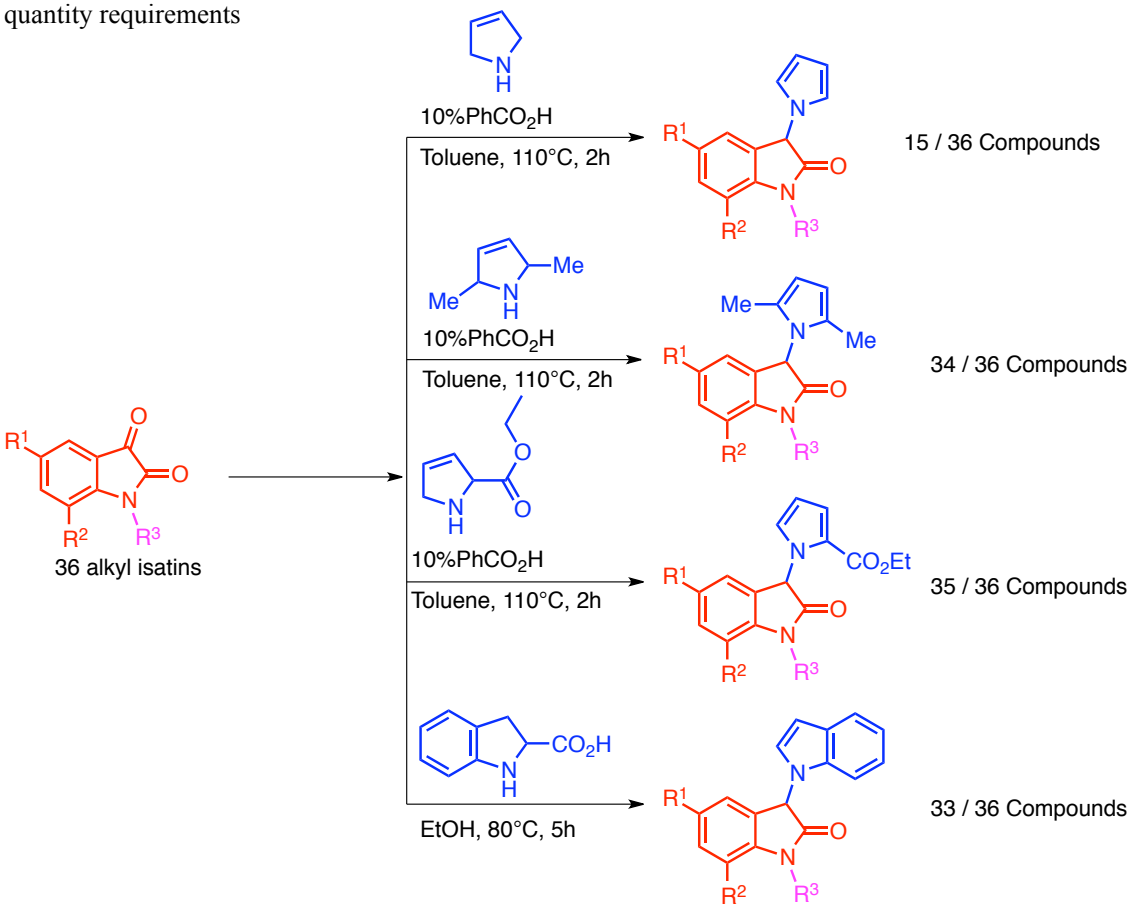


Table 3-2.6: Summary of library synthesis. Fractions indicate number of compounds that pass purity and quantity requirements



Completion of the library generated 114 compounds. Compounds isolated in >90% purity and quantities of 5 mg or higher are considered as passing. It is of note that the products of redox amination using pyrroline (Table 3-2.2) exhibit a large drop in purity. The exact cause of this loss in purity was not determined. It is important to note that this does not mean that the reaction did not work or that the desired product was not synthesized, it only means that the purity of the product and the mass recovered did not meet the standards to pass. Redox amination with the pyrroline-2-ethyl ester (Table 3-2.3), 2,5 dimethyl pyrroline (Table 3-2.4), and indoline-2-carboxylic acid (Table 3-2.5) were much more successful at generating compounds at a passing rate. Overall, 118 of the 144 compounds synthesized passed and have been added to the added to the Kansas University NIH Center for Chemical Methodologies and Library Development (KU CMLD) collection and has been submitted to the National Institutes of Health Molecular Library Screening Center Network (MLSCN) for evaluation in a broad range of assays.

In conclusion, we have published a methodology for the synthesis of oxindoles containing an N1-C3 bisindole linkage. This method is redox neutral and produces only water and CO_2 as by-products. This redox amination is applicable to range of isatins and to demonstrate this we have synthesized a library of compounds containing this linkage.

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[2] (a) Discovery Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. New Type of Trimeric and Pentameric Indole Alkaloids from Psychotria rostrata *Org. Lett.* **2004**, *6*, 2945 (b) Total synthesis Matsuda, Y.; Kitajima, M.; Takayama, H. First Total Synthesis of Trimeric Indole Alkaloid, Psychotrimine *Org. Lett.* **2008**, *10*,

125; (c) Newhouse, T.; Baran, P. S. Total synthesis of (¬±)-psychotrimine *Chemtracts* **2008**, *21*, 67; (d) Biological activity Schallenberger, M. A.; Newhouse, T.; Baran, P. S.; Romesberg, F. E. The psychotrimine natural products have antibacterial activity against Gram-positive bacteria and act via membrane disruption *J. Antibiot.* **2010**, (e) *63*, 685 enantiospecific total syntheses Takahashi, N.; Ito, T.; Matsuda, Y.; Kogure, N.; Kitajima, M.; Takayama, H. Determination of absolute configuration of trimeric indole alkaloid, psychotrimine, by first asymmetric total synthesis *Chem. Commun.* **2010**, *46*, 2501;(f) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine *Angew. Chem., Int. Ed.* **2011**, *50*, 2716

3 Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. Total Synthesis Guided Structure Elucidation of (+)-Psychotetramine *Angew. Chem., Int. Ed.* **2011**, *50*, 2716

[4] Gaich, T.; Baran, P. S.Aiming for the Ideal Synthesis *J. Org. Chem.* **2010**, *75*, 4657; Newhouse, T.; Lewis, C. A.; Eastman, K. J.; Baran, P. S.Scalable Total Syntheses of N-Linked Tryptamine Dimers by Direct Indole-Aniline Coupling: Psychotrimine and Kapakahines B and F *J. Am. Chem. Soc.* **2010**, *132*, 7119

[5] Peng, Y.; Luo, L.; Yan, C.-S.; Zhang, J.-J.; Wang, Y.-W Ni-Catalyzed Reductive Homocoupling of Unactivated Alkyl Bromides at Room Temperature and Its Synthetic Application. *J. Org. Chem.* **2013**, *78*, 10960.

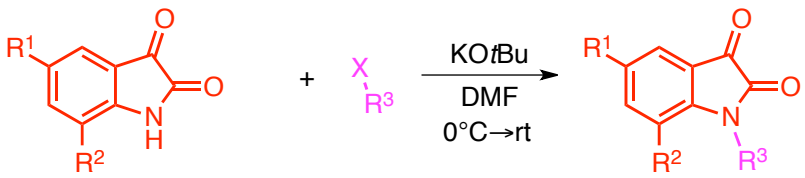
Chapter 3 Supporting Information

General Information

For library synthesis all chemicals were used as received from commercial sources. Anhydrous organic solvents (e.g. EtOAc, $CHCl_3$, MeOH, EtOH, MeCN, DMF, hexane, toluene, etc.) were used for the reactions. All the diversification reactions were carried out in Mettler Toledo® Miniblock or microwave vials. All air and moisture sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere using standard gas tight syringes, cannula, and septa. Stirring was achieved with oven-dried, magnetic stir bars. Analytical thin layer chromatography (TLC) was performed using commercially prepared polyester backed silica gel plates (200 microns), and visualization was effected with short wavelength UV light (254 nm). Flash column chromatography was carried out using Teledyne Isco CombiFlash R_f employing normal phase disposable columns. Infrared (IR) spectra were acquired as thin films on a PerkinElmer Spectrum 100 FT-IR spectrometer, and the absorptions are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz/500 MHz/600 MHz ^1H, 125 MHz ^{13}C). Chemical shifts are reported in parts per million (ppm), and referenced to the solvent: $CDCl_3$ with TMS as internal reference (0.0 ppm for ^1H and 0.0 ppm for ^{13}C) and DMSO-d_6. Coupling constants (J) are reported in Hertz (Hz). Purification via preparative chromatography was achieved utilizing a Waters X-Bridge C18 column (19 x 150 mm, 5 µm, with 19 x 10 mm guard column) at a flow rate of 20 mL/min. Samples were diluted in DMSO and purified using an elution mixture of water and MeCN, running a concentration gradient which increased by 20% MeCN over a 4 minute period. The starting and ending points of the corresponding preparative

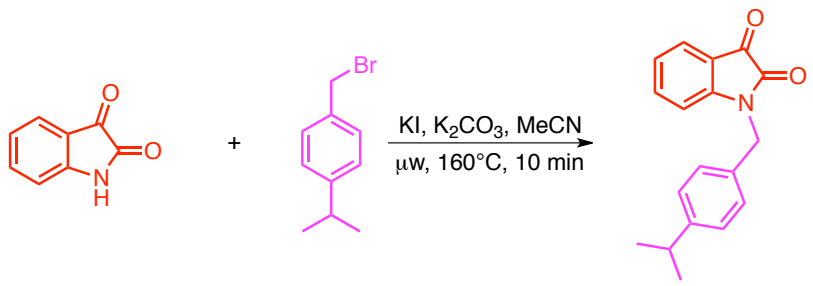
MeCN/water gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis after preparative chromatography utilized a Waters Acquity system with UV-detection and mass-detection (Waters LCT Premier). The analytical method conditions included a Waters Aquity BEH C18 column (2.1 x 50 mm, 1.7 um) and elution with a linear gradient of 5% water to 100% MeCN at 0.6 mL/min flow rate. The purity of each sample was determined using UV peak area detected at 214 nm wavelength. High resolution mass spectra for the starting benzisoxazole blocks were recorded using QTOF mass spectrometer (APCI at a voltage of 70 eV). High resolution mass spectra for the diversified products were recorded using time-of-flight mass spectrometer.

General procedure for synthesizing N-1 substituted isatins:



Alkylation of isatins using Miniblock - Bohdan MiniBlock® XT solution phase synthesizer hosting 6 reaction vessels was utilized for the parallel synthesis. A stock solution of 1 M solution of potassium *tert* butoxide in THF was prepared in DMF (1 mmol/2 mL). Six stock solutions of premixed alkyl halide (1.2 mmol) and substituted isatins (1.0 mmol) in 1 mL of DMF were prepared. Potassium *tert* butoxide solution (4

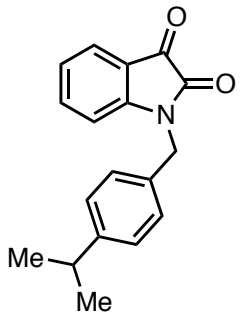
mL) was placed into 2 x 3 reactor tubes and cooled down to 0 °C. After 5 mins the premixed stock solutions were added dropwise to each reactor tube at 0 °C. The resultant brown reaction mixture was stirred at 0 °C for another 30 mins and then stirred at room tempreture for 16 h. The solvent was removed (Genevac) and crude was subjected to normal phase flash silica gel column chromatography to obtain the desired product in 0-50% yield.



Microwave Irradiation: 0.147g Isatin (1 mmol), 0.276g of K_2CO_3 (2.0 mmol), 16mg of KI (0.1 mmol) and 0.234g of 4-isopropyl benzyl bromide (1.1 mmol) were dissolved in acetonitrile (2 mL) and microwave irradiated in a 5 mL microwave vial for 10 mins at 160 °C. The reaction mixture was partitioned in EtOAc and H_2O (10 mL) and the combined organic layers was dried over Na_2SO_4 and concentrated in Genevac. The products were analysed by LCMS and ^{1}HNMR and showed with >90% purity by ELSD and 254 nM UV analysis.

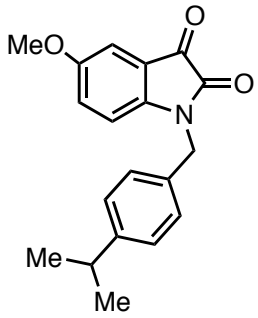
Spectral data for new isatins

3.1a) 1-(4-isopropylbenzyl)indoline-2,3-dione



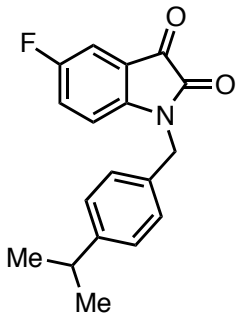
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.49 (td, *J* = 7.9, 1.3 Hz, 1H), 7.27 (s, 4H), 7.26 (s, 4H), 7.23 – 7.17 (m, 2H), 7.09 (td, *J* = 7.5, 0.9 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.89 (s, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H**).** **^{13}C NMR (125 MHz, $CDCl_3$)** δ 183.37, 158.24, 150.86, 148.94, 138.28, 131.80, 127.53, 127.09, 125.39, 123.78, 117.67, 111.03, 76.76, 43.81, 33.78, 23.90. **FTIR (neat)**: 2960, 2920, 1738, 1612, 1470, 1349,1176 cm^{-1}. **HRMS calculated**: $C_{18}H_{17}NO_2$ $(M+H)^+$ 280.1338; found 280.1352 (TOF MS ES^+).

3.1b) 1-(4-isopropylbenzyl)-5-methoxyindoline-2,3-dion



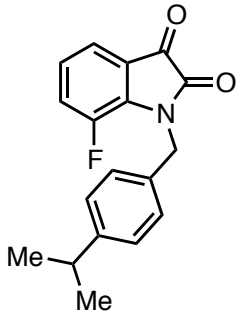
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.26 – 7.23 (m, 2H), 7.21 – 7.17 (m, 2H), 7.15 (d, *J* = 2.7 Hz, 1H), 7.04 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.86 (s, 2H), 3.77 (s, 3H), 2.88 (hept, *J* = 7.1 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 7H) **^{13}C NMR (125 MHz, $CDCl_3$)** δ 183.76, 158.33, 156.49, 148.90, 144.77, 131.89, 127.50, 127.07, 124.70, 118.08, 112.07, 109.45, 55.93, 43.82, 33.79, 23.91. **FTIR (neat)** : 2960, 2920, 1732, 1622, 1489, 1437,1219 cm^{-1}. **HRMS calculated**: $C_{19}H_{19}NO_3$ $(M+H)^+$ 310.1443; found 310.1466 (TOF MS ES^+).

3.1d) 5-fluoro-1-(4-isopropylbenzyl)indoline-2,3-dione



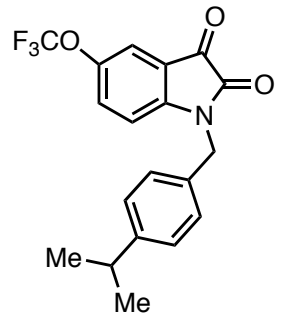
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, J = 6.5, 2.7 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.23 – 7.17 (m, 3H), 6.76 (dd, J = 8.6, 3.6 Hz, 1H), 4.89 (s, 2H), 2.89 (hept, J = 6.8 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.80, 159.28 (d, J_{CF} = 246.81 Hz), 157.99 (d, J_{CF} = 1.5 Hz), 149.10, 146.84, 131.41, 127.48, 127.16, 124.60 (d, J_{CF} = 24.1 Hz), 118.25 (d, J_{CF} = 7.1 Hz), 112.38 (d, J_{CF} = 24.3 Hz), 112.23 (d, J_{CF} = 7.1 Hz), 43.94, 33.79, 23.89. **FTIR (neat)** : 2961, 2924, 2853, 1735, 1623, 1484, 1332,1218 cm^{-1}. **HRMS calculated**: $C_{18}H_{16}FNO_2$ $(M+H)^+$ 298.1243; found 298.1254 (TOF MS ES$^+$).

3.1e) 7-fluoro-1-(4-isopropylbenzyl)indoline-2,3-dione



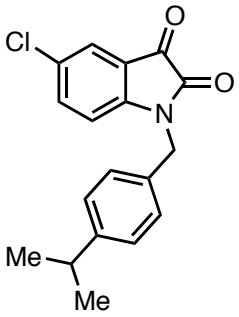
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.4, 1.1 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 7.21 – 7.17 (m, 2H), 7.06 (ddd, J = 8.3, 7.4, 3.9 Hz, 1H), 5.03 (s, 2H), 2.88 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.50, 158.04, 147.95 (d, J_{CF} = 248.8 Hz), 136.85 (d, J_{CF} = 9.0 Hz), 133.00, 127.94 (d, J_{CF} = 1.6 Hz), 126.87, 126.60 (d, J_{CF} = 20.2 Hz), 124.67 (d, J_{CF} = 5.6 Hz), 121.47 (d, J_{CF} = 3.4 Hz), 120.36 (d, J_{CF} = 2.7 Hz), 45.72, 33.79, 23.90. **FTIR (neat)** : 3039, 2958, 1732, 1623, 1461, 1345,1172 cm^{-1}. **HRMS calculated**: $C_{18}H_{16}FNO_2$ $(M+H)^+$ 298.1243; found 298.1254 (TOF MS ES$^+$).

3.1f) 1-(4-isopropylbenzyl)-5-(trifluoromethoxy)indoline-2,3-dione



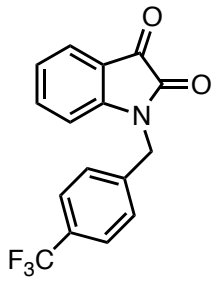
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 1.5 Hz, 1H), 7.35 (ddd, J = 8.5, 2.5, 0.9 Hz, 1H), 7.26 – 7.20 (m, 4H), 6.84 (d, J = 8.6 Hz, 1H), 4.90 (s, 2H), 2.89 (hept, J = 6.7 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.35, 157.88, 149.24, 149.13, 131.22, 130.96, 127.53, 127.24, 126.93, 126.86, 118.46, 118.15, 112.12, 44.03, 33.80, 23.89. **FTIR (neat)** : 2964, 2924, 1744, 1622, 1485, 1255,1218 cm^{-1}. **HRMS calculated**: $C_{19}H_{16}F_3NO_3$ $(M+H)^+$ 364.1161; found 364.1179

3.1c) 5-Chloro-1-(4-isopropylbenzyl)indoline-2,3-dione



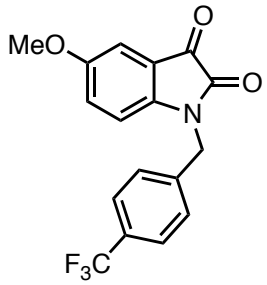
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 8.3, 2.3 Hz, 1H), 7.25 – 7.18 (m, 4H), 6.76 (d, J = 8.4 Hz, 1H), 4.89 (s, 2H), 2.89 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 7.0 Hz, 6H). **^{13}C NMR (125MHz, $CDCl_3$)** δ 182.36, 157.67, 149.15, 137.63, 131.30, 129.66, 127.48, 127.18, 125.27, 118.47, 112.34, 43.95, 33.79, 23.89. **FTIR (neat)** : 2961, 2873, 1739, 1608, 1473, 1444,1330 cm^{-1}. **HRMS calculated**: $C_{18}H_{16}ClNO_2$ $(M+H)^+$ 314.0948; found 314.0958

3.4a)1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



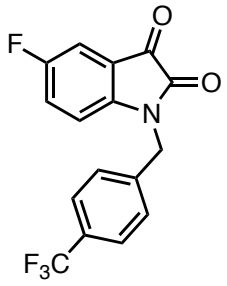
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.59 (m, 3H), 7.51 (td, *J* = 7.8, 1.3 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.13 (td, *J* = 7.6, 0.8 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 4.99 (s, 2H**).** **^{13}C NMR (100 MHz, $CDCl_3$)** δ 182.76, 158.26, 150.27, 138.60, 138.43, 130.60 (q, J_{CF} = 32.8 Hz), 127.69, 126.11 (q, J_{CF} = 3.7 Hz), 125.70, 123.85 (q, J_{CF} = 272.1 Hz), 124.21, 117.74, 110.68, 43.60. **HRMS calculated**: $C_{16}H_{10}F_3NO_2$ $(M+H)^+$ 306.0742; found 306.0757

3.4b) 5-methoxy-1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



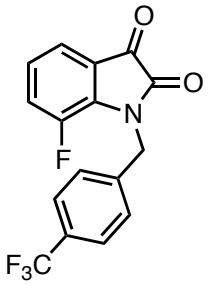
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 3H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.96 (s, 2H), 3.79 (s, 3H**).** **^{13}C NMR (100 MHz, $CDCl_3$)** δ 183.16, 158.38, 156.78, 144.09, 138.72, 130.55 (q, J_{CF} = 32.7 Hz), 127.67, 126.09 (q, J_{CF} = 3.8 Hz), 124.76, 123.85 (d, J_{CF} = 272.4 Hz),118.18, 111.72, 109.84, 55.99, 43.61. **FTIR (neat)** : 2924, 2845, 1730, 1620, 1489, 1321, 1163,1110 cm^{-1}. **HRMS calculated**: $C_{17}H_{12}F_3NO_3$ $(M+H)^+$ 336.0848; found 336.0847

3.4d)5-fluoro-1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



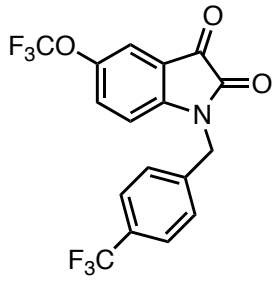
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.36 (dd, J = 6.4, 2.8 Hz, 1H), 7.23 (td, J = 8.6, 2.7 Hz, 1H), 6.68 (dd, J = 8.6, 3.6 Hz, 1H), 4.99 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.19, 159.50 (d, J_{CF} = 246.9 Hz), 158.02, 146.25(d, J_{CF} = 2.26 Hz), 138.22, 131.12, 130.74 (q, J_{CF} = 32.7 Hz), 127.65, 127.01 (d, J_{CF} = 6.4 Hz), 126.20 (q, J_{CF} = 3.6 Hz), 126.16, 125.89, 124.88, 124.69, 121.61 (q, J = 272.2 Hz), 118.35 (d, J_{CF} = 6.7 Hz), 112.79 (d, J_{CF} = 23.9 Hz), 111.87 (d, J_{CF} = 7.3 Hz), 43.72. **FTIR (neat)** : 2917, 2850,1739, 1623, 1485, 1323, 1266,1167, 1119 cm^{-1}. **HRMS calculated**: $C_{16}H_9F_4NO_2$ $(M+H)^+$ 324.0648; found 324.063

3.4e) 7-fluoro-1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



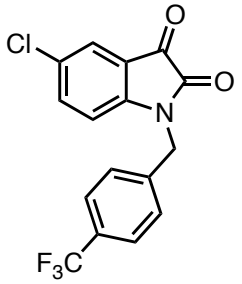
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.56 – 7.47 (m, 3H), 7.34 (ddd, J = 11.3, 8.4, 1.1 Hz, 1H), 7.13 (ddd, J = 8.4, 7.4, 4.0 Hz, 1H), 5.15 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 181.89, 158.00, 147.82 (d, J_{CF} = 248.1 Hz), 139.54, 136.26 (d, J_{CF} = 9.0 Hz), 130.50 (q, J_{CF} = 32.4 Hz), 128.06 (d, J_{CF} = 1.5 Hz), 126.67 (d, J_{CF} = 19.8 Hz), 125.87 (q, J_{CF} = 3.7 Hz), 125.11 (d, J_{CF} = 6.1 Hz), 123.90 (q, J_{CF} = 272.4 Hz), 121.73 (d, J_{CF} = 3.2 Hz), 120.30 (d, J_{CF} = 2.3 Hz), 45.49. **FTIR (neat)** : 3040, 2920, 2851, 1733, 1620, 1325, 1170, 1067 cm^{-1}. **HRMS calculated**: $C_{16}H_9F_4NO_2$ $(M+H)^+$ 324.0648; found 324.0582

3.4f) 5-(trifluoromethoxy)-1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



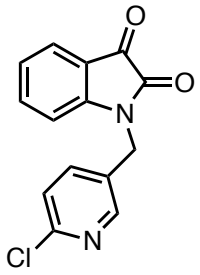
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 1.2 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.37 (ddd, *J* = 8.6, 2.6, 0.8 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 5.01 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 181.76, 157.89, 148.51, 145.57, 138.02, 131.12, 130.84 (q, J = 32.8 Hz), 127.70, 126.26 (q, J = 3.7 Hz), 123.76 (q, J = 272.3 Hz), 120.32 (q, J = 258.6 Hz), 118.79, 118.23, 111.80, 43.79. **FTIR (neat)** : 2924, 1743, 1621, 1486, 1325,1256, 1168 cm^{-1}. **HRMS calculated**: $C_{17}H_9F_6NO_3$ $(M+H)^+$ 390.0565; found 390.0572 .

3.4c) 5-Chloro-1-(4-(trifluoromethyl)benzyl)indoline-2,3-dione



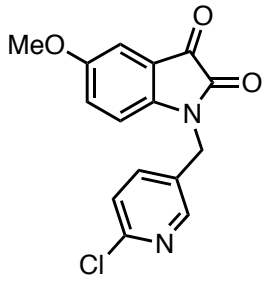
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 3H), 7.50 – 7.38 (m, 3H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.99 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 181.77, 157.71, 148.45, 138.14, 137.80, 130.79 (q, J_{CF} = 33.0 Hz), 130.16, 127.67, 126.22 (q, J_{CF} = 3.7 Hz), 125.62, 123.78 (q, J_{CF} = 272.1 Hz), 118.55, 111.96, 43.73. **FTIR (neat)** : 2920, 1740, 1609, 1474, 1322,1117, 1066 cm^{-1}.**HRMS calculated**: $C_{16}H_9ClF_3NO_2$ $(M+H)^+$ 340.0352; found 340.0359

3.3a) 1-((6-Chloropyridin-3-yl)methyl)indoline-2,3-dione



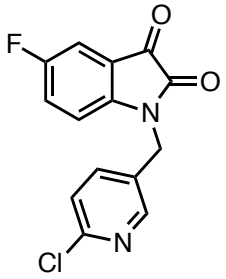
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.5 Hz, 1H), 7.66 (ddd, *J* = 7.5, 3.9, 1.9 Hz, 2H), 7.55 (td, *J* = 7.8, 1.4 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.15 (td, *J* = 7.5, 0.8 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 2H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.45, 158.23, 151.68, 149.76, 148.83, 138.51, 138.24, 129.46, 125.88, 124.91, 124.41, 117.73, 110.36, 40.87. **FTIR (neat)** : 2917, 2849, 1738, 1612, 1468, 1342,1096 cm^{-1}. **HRMS calculated**: $C_{14}H_9ClN_2O_2$ $(M+H)^+$ 273.0431; found 273.0431

3.3b) 1-((6-Chloropyridin-3-yl)methyl)-5-methoxyindoline-2,3-dione



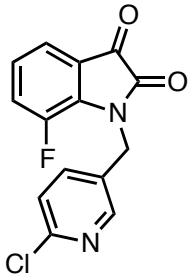
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 7.08 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 4.90 (s, 2H), 3.79 (s, 3H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 182.82, 158.33, 156.87, 151.62, 148.79, 143.53, 138.19, 129.55, 124.87, 118.19, 111.38, 110.05, 56.00, 40.88. **FTIR (neat)** : 2925, 2841, 1730, 1622, 1599, 1489, 1335,1275 cm^{-1}. **HRMS calculated**: $C_{15}H_{11}ClN_2O_3$ $(M+H)^+$ 303.0536; found 303.0543 (TOF MS ES^+).

3.3d) 1-((6-Chloropyridin-3-yl)methyl)-5-fluoroindoline-2,3-dione



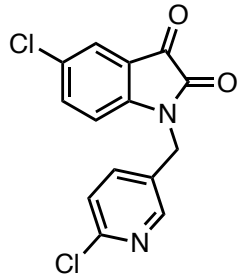
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.5 Hz, 1H), 7.65 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.27 (td, *J* = 8.5, 2.7 Hz, 1H), 6.76 (dd, *J* = 8.6, 3.5 Hz, 1H), 4.93 (s, 2H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 181.88, 159.55 (d, J_{CF} = 247.1 Hz), 157.99 (d, J_{CF} = 1.5 Hz), 151.79, 148.77, 145.76, 138.18, 129.16, 124.86 (d, J_{CF} = 26.2 Hz), 118.38 (d, J_{CF} = 7.1 Hz), 112.98 (d, J_{CF} = 24.4 Hz), 111.58 (d, J_{CF} = 7.2 Hz), 41.00. **FTIR (neat)** : 3055, 2925, 1732, 1622, 1482, 1331,1265 cm^{-1}. **HRMS calculated**: $C_{14}H_8ClFN_2O_2$ $(M+H)^+$ 291.0337; found 291.0344 (TOF MS ES$^+$).

3.3e) 1-((6-Chloropyridin-3-yl)methyl)-7-fluoroindoline-2,3-dione



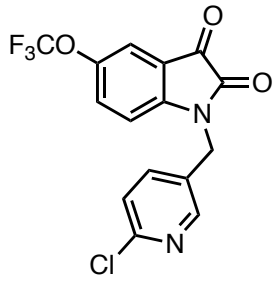
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.69 (td, *J* = 8.4, 2.5 Hz, 1H), 7.47 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.11 (ddd, *J* = 8.4, 7.4, 4.0 Hz, 1H), 5.05 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 181.59, 157.99, 151.59, 149.68 (d, J_{CF} = 235.9 Hz), 149.33 (d, J_{CF} = 2.9 Hz), 148.25, 146.77, 138.70, 137.64, 135.82 (d, J_{CF} = 8.7 Hz), 130.36, 126.69 (d, J_{CF} = 19.9 Hz), 125.30 (d, J_{CF} = 5.8 Hz), 124.60, 124.16, 121.86 (d, J_{CF} = 3.0 Hz), 120.31, 120.29, 61.88, 42.89. **FTIR (neat)** : 2924, 2854, 1741, 1627, 1460, 1341,1233,1105 cm^{-1}. **HRMS calculated**: $C_{14}H_8ClFN_2O_2$ $(M+H)^+$ 291.0337; found 291.0351 (TOF MS ES$^+$).

3.3c) 5-Chloro-1-((6-chloropyridin-3-yl)methyl)indoline-2,3-dione



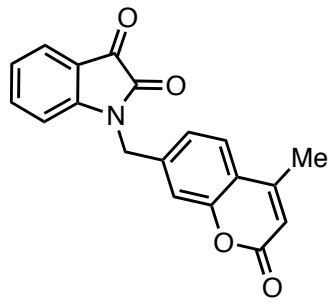
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.93 (s, 2H**). ^{13}C NMR (125 MHz, $CDCl_3$)** δ 181.45, 157.67, 151.84, 148.77, 147.95, 138.17, 137.85, 130.34, 129.06, 125.79, 124.98, 118.53, 111.63, 41.01. **FTIR (neat)** : 2922, 2852, 1740, 1610, 1464, 1331, 1260,1103 cm^{-1}. **HRMS calculated**: $C_{14}H_8Cl_2N_2O_2$ $(M+H)^+$ 307.0041; found 307.0046 (TOF MS ES^+).

3.3f) 1-((6-Chloropyridin-3-yl)methyl)-5-(trifluoromethoxy)indoline-2,3-dione



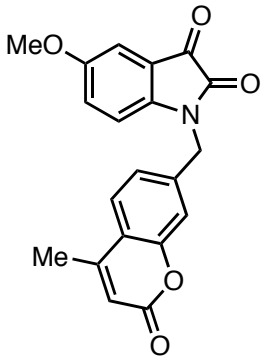
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 1.9 Hz, 1H), 7.65 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.53 (d, *J* = 1.3 Hz, 1H), 7.41 (ddq, *J* = 8.6, 2.4, 0.8 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 4.94 (s, 2H**). ^{13}C NMR (100 MHz, $CDCl_3$)** δ 181.44, 157.87, 151.98, 148.81, 148.05, 145.72 (q, J_{CF} = 2.1 Hz), 138.20, 131.17, 128.98, 125.05, 120.32 (q, J_{CF} = 258.9 Hz), 118.97, 118.31, 111.48, 41.09. **FTIR (neat)** : 3055, 1743, 1621, 1485, 1255,1173 cm^{-1}. **HRMS calculated**: $C_{15}H_8ClF_3N_2O_3$ $(M+1)^+$ 357.0254; found 357.0251 (TOF MS ES^+).

3.6a) 1-((4-methyl-2-oxo-2H-chromen-7-yl)methyl)indoline-2,3-dione



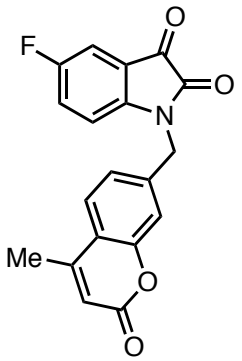
^{1}H NMR (500 MHz, $CDCl_3$) 7.59 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.44 (td, *J* = 7.8, 1.3 Hz, 1H), 7.20 (m, 2H), 7.07 (td, *J* = 7.6, 0.7 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.23 (d, *J* = 1.2 Hz, 1H), 4.95 (s, 2H), 2.35 (d, *J* = 1.3 Hz, 3H)**.^{13}C NMR (126 MHz, $CDCl_3$)** 182.69, 160.32, 158.21, 153.77, 151.91, 150.18, 138.90, 138.47, 125.76, 125.58, 124.28, 123.05, 119.81, 117.72, 115.84, 115.39, 110.68, 43.49, 18.66. **HRMS calculated**: $C_{19}H_{13}NO_4$ $(2M+H)^+$ 639.1767; found 639.178 (TOF MS ES^+).

3.6b) 5-methoxy-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)indoline-2,3-dione



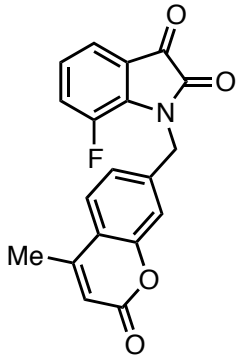
^{1}H NMR (500 MHz, DMSO) 7.81 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.25 ? 7.18 (m, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 1.2 Hz, 1H), 5.06 (s, 2H), 3.81 (s, 3H), 2.48 (d, *J* = 1.2 Hz, 3H **^{13}C NMR (126 MHz, DMSO)** 183.56, 160.17, 159.00, 156.28, 153.58, 153.54, 144.14, 140.86, 126.20, 123.87, 123.72, 119.31, 118.94, 115.56, 114.61, 112.43, 109.79, 56.35, 42.85, 18.55.
HRMS calculated: $C_{20}H_{15}NO_5$ $(M+H)^+$ 350.1028; found 350.1038 (TOF MS ES^+).

3.6b) 5-methoxy-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)indoline-2,3-dione



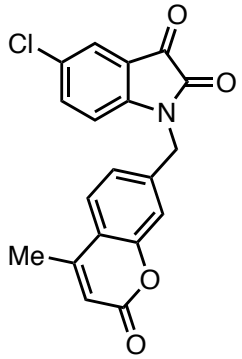
^{1}H NMR (500 MHz, DMSO) 7.75 (d, *J* = 8.2 Hz, 1H), 7.56 (s, 1H), 7.52 ? 7.49 (m, 1H), 7.33 (dd, *J* = 11.5, 3.0 Hz, 1H), 7.06 ? 7.00 (m, 1H), 6.92 (dd, *J* = 8.6, 3.7 Hz, 1H), 6.38 (s, 1H), 5.03 (s, 2H), 2.42 (s, 3H)**. ^{13}C NMR (126 MHz, DMSO)** 182.67, 160.17, 153.59, 153.55, 146.60, 140.60, 126.18, 124.15, 123.95, 123.74, 119.33, 115.53, 114.62, 112.71, 112.65, 112.06, 111.86, 42.92, 18.55.**HRMS calculated**: $C_{19}H_{12}FNO_4$ $(M+H)^+$ 338.0829; found 338.0853 (TOF MS ES^+).

3.6e) 7-fluoro-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)indoline-2,3-dione



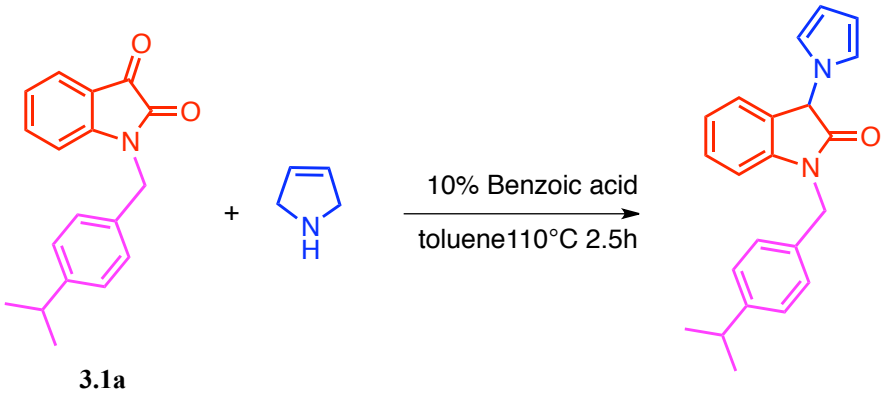
^{1}H NMR (500 MHz, DMSO) 7.82 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 1.3 Hz, 1H), 7.54 (dd, *J* = 7.8, 4.4 Hz, 2H), 7.52 ? 7.49 (m, 1H), 7.23 ? 7.19 (m, 1H), 6.44 (d, *J* = 1.2 Hz, 1H), 5.14 (s, 2H), 2.50 (dd, *J* = 4.6, 1.3 Hz, 3H). **^{13}C NMR (126 MHz, DMSO)** 182.07, 160.21, 159.05, 153.66, 153.60, 148.51, 146.56, 141.81, 126.10, 125.96, 125.81, 124.96, 123.10, 121.18, 119.16, 114.73, 114.52, 44.97, 18.56.**HRMS calculated**: $C_{19}H_{12}FNO_4$ $(M+H)^+$ 338.0829; found 338.0843 (TOF MS ES^+).

3.6c)5-Chloro-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)indoline-2,3-dione



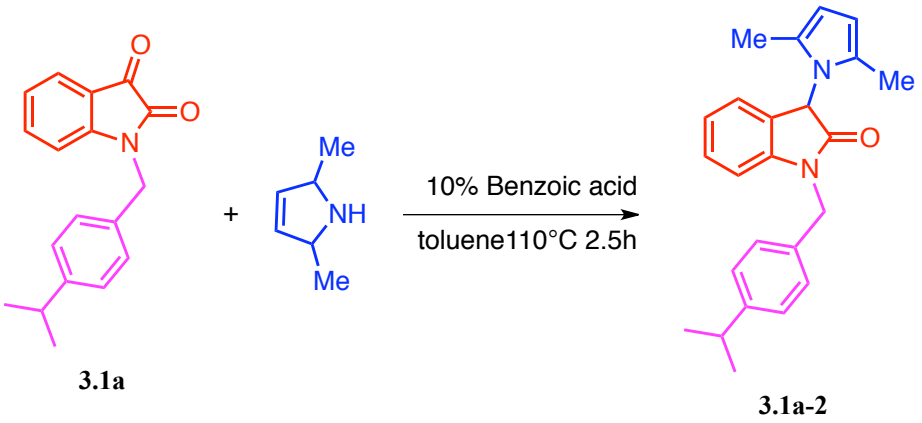
^{1}H NMR (500 MHz, DMSO) 7.75 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 1H), 5.04 (s, 2H), 2.42 (s, 3H). **^{13}C NMR (126 MHz, DMSO)** 182.18, 160.17, 158.81, 153.60, 153.56, 148.89, 140.50, 137.03, 128.01, 126.17, 124.39, 123.73, 119.97, 119.33, 115.48, 114.62, 113.03, 42.93, 18.56.**HRMS calculated**: $C_{19}H_{12}ClNO_4$ $(2M+H)^+$ 707.0988; found 707.1002 (TOF MS ES^+).

Redox amination:



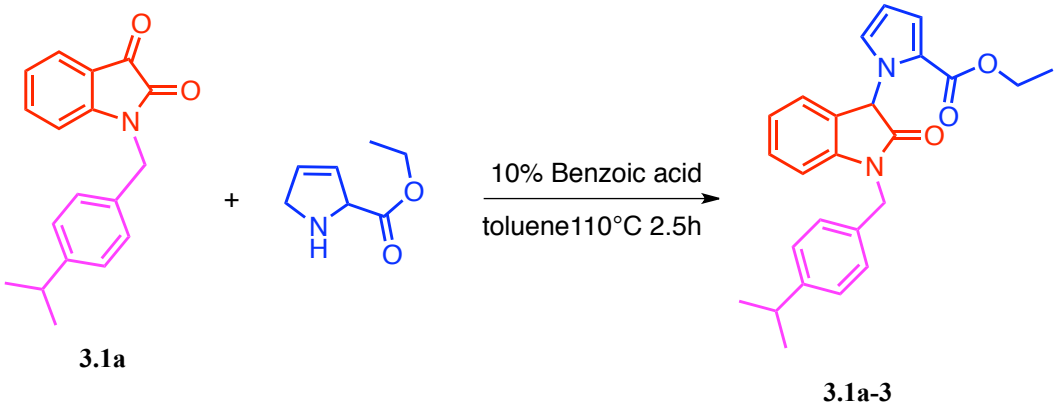
3.1a **3.1a-1**

83.8 mg of isatin **3.1a** (0.3 mmol), 35 µL of 3-pyrroline (0.45 mmol) and 4 mg of benzoic acid (0.03 mmol) were dissolved in toulene (2 mL) in a 5ml microwave vial. The resultant solution was heated up to 110 °C for 2.5 h. Obtained crude was concentrated in Genevac and analyzed by LCMS. Purification by mass-directed Preparative HPLC afforded 32.3 mg of **3.1a-1** as a colored solid (10%) with >90% purity by ELSD and 254 nM UV analysis. (15/36 Compounds passed the purity and quantity requirement with overall 41% success rate)



3.1a **3.1a-2**

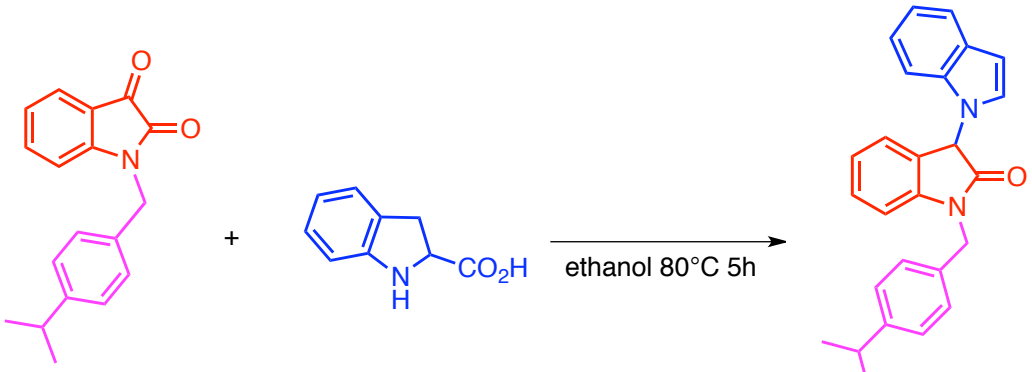
83.8 mg of isatin **3.1a** (0.3 mmol), 53 µL 2,5-dimethyl-3-pyrroline (0.45 mmol) and 4mg of benzoic acid (0.03 mmol) were dissolved in toulene (2 mL) in a 5mL microwave vial. The resultant solution was heated up to 110 °C for 2.5 h. Obtained crude was concentrated in Genevac and analyzed by LCMS. Purification by mass-directed Preparative HPLC afforded 16 mg of **3.1a-2** as a colored solid (5%) with >90% purity by ELSD and 254 nM UV analysis. (34/36 Compounds passed the purity and quantity requirement with overall 94% success rate)



3.1a **3.1a-3**

83.8 mg of isatin **3.1a** (0.3 mmol), 64 mg of ethyl 2,5-dihydro-1*H*-pyrrole-2-carboxylate (0.45 mmol)) and 4mg of benzoic acid (0.03 mmol) were dissolved in toulene in a 5mL microwave vial. The resultant solution was heated up to 110 °C for 2.5 h. Obtained crude was concentrated in Genevac and analyzed by LCMS. Purification by mass-directed Preparative HPLC afforded 50.3mg **3.1a-3** as a colored solid (42%) with >90% purity by

ELSD and 254 nM UV analysis. (35/36 Compounds passed the purity and quantity requirement with overall 97% success rate)



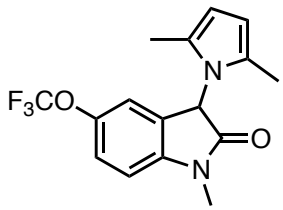
3.1a **3.1a-4**

83.8 mg of isatin **3.1a** (0.3 mmol) and 73 mg indoline-2-carboxylic acid (0.45 mmol) were dissolved in EtOH (2 mL) in a 5ml microwave vial. The resultant solution was heated up to 80 °C for 5 h. Obtained crude was concentrated in Genevac and analyzed by LCMS. Purification by mass-directed Preparative HPLC afforded 35.2 mg og **3.1a-4** as colored solids (27%) with >90% purity by ELSD and 254 nM UV analysis. (34/36 Compounds passed the purity and quantity requirement with overall 94% success rate)

Spectral data for library compounds

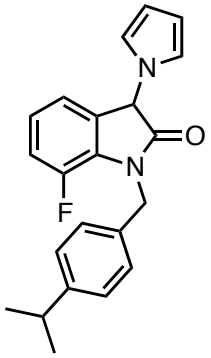
Reported here is a random sampling of 20 of the compounds made.

3.5f-2): 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-methyl-5-(trifluoromethoxy)indolin-2-one



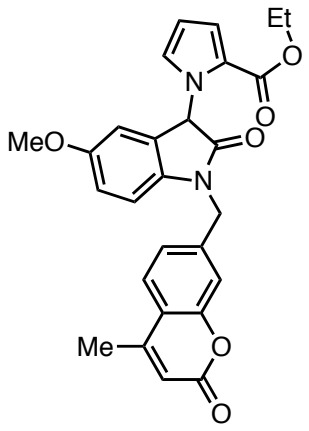
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dt, *J* = 2.2, 1.0 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 5.88 (dd, *J* = 3.3, 1.1 Hz, 1H), 5.78 (dd, *J* = 3.2, 1.2 Hz, 1H), 5.60 (s, 1H), 3.31 (s, 3H), 2.40 (s, 3H), 1.60 (s, 3H)**.** **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.97, 141.89, 129.28, 127.56, 127.19, 122.75, 118.28, 109.03, 107.70, 106.63, 56.68, 26.76, 12.89, 12.29, 0.00. **FTIR (neat)** : 2927, 1725, 1621, 1494, 1248 cm^{-1}. **HRMS calculated**: $C_{16}H_{15}F_3N_2O_2$ $(M+H)^+$ 325.1164; found 325.1160

3.1e-1) :7-fluoro-1-(4-isopropylbenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one

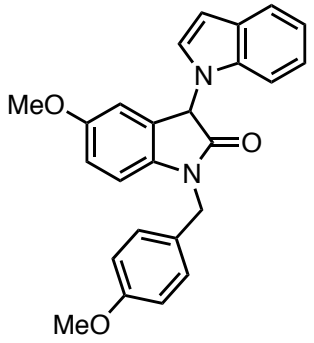


3.1e-1) :7-fluoro-1-(4-isopropylbenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.19 – 7.14 (m, 2H), 7.10 – 6.96 (m, 3H), 6.67 (t, J = 2.1 Hz, 2H), 6.27 – 6.22 (m, 2H), 5.54 (t, J = 0.9 Hz, 1H), 5.11 – 4.93 (m, 2H), 2.87 (hept, J = 6.9 Hz, 1H), 1.22 (d, J = 6.9 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.28, 147.52 (d, J_{CF} = 246.4 Hz), 133.91, 130.09 (d, J_{CF} = 9.5 Hz), 127.75 (d, J_{CF} = 1.4 Hz), 127.51 (d, J_{CF} = 3.4 Hz), 126.74, 123.95 (d, J_{CF} = 6.6 Hz), 121.19 (d, J_{CF} = 3.5 Hz), 120.24, 118.28 (d, J_{CF} = 19.6 Hz), 109.70, 77.27, 60.39 (d, J_{CF} = 2.4 Hz), 45.50 (d, J_{CF} = 4.8 Hz), 33.77, 23.92 **HRMS calculated**: $C_{22}H_{21}FN_2O$ $(M+H)^+$ 349.1716; found 349.1702

3.6b-3) Ethyl 1-(5-methoxy-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)-2-oxoindolin-3-yl)-1*H*-pyrrole-2-carboxylate ^{1}H NMR

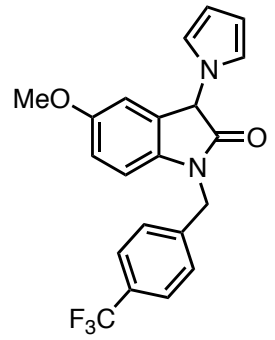


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 13.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.78 (d, *J* = 6.9 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.55 (s, 1H), 6.28 (s, 1H), 6.26 – 6.19 (m, 1H), 5.06 – 4.89 (m, 2H), 4.37 (q, *J* = 8.2, 7.6 Hz, 2H), 3.72 (s, 3H), 2.42 (d, *J* = 1.4 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.50, 161.76, 160.51, 156.63, 153.73, 152.03, 140.04, 135.65, 126.76, 125.42, 125.36, 123.43, 123.07, 119.52, 118.46, 115.79, 115.16, 114.50, 112.27, 110.06, 109.88, 60.27, 58.30, 55.82, 43.62, 41.00, 18.65, 14.43. **HRMS calculated**: $C_{27}H_{24}N_2O_6$ $(M+H)^+$ 473.1713; found 473.1718



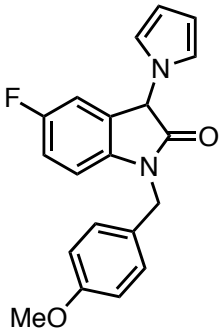
3.2b-4): 3-(1*H*-indol-1-yl)-5-methoxy-1-(4-methoxybenzyl)indolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 1H), 7.34 – 7.27 (m, 2H), 7.17 – 6.97 (m, 4H), 6.89 – 6.85 (m, 2H), 6.82 – 6.79 (m, 2H), 6.76 (dt, *J* = 2.1, 1.1 Hz, 1H), 6.59 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.89 (d, *J* = 1.2 Hz, 1H), 5.05 – 4.76 (m, 2H), 3.80 (s, 3H), 3.78 (d, *J* = 7.4 Hz, 1H), 3.66 (s, 3H**). ^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.30, 159.28, 156.40, 136.27, 129.26, 129.15, 125.87, 122.12, 121.22, 120.12, 114.82, 114.38, 114.23, 111.84, 110.37, 109.87, 103.12, 55.75, 55.30, 43.82, 41.00.. **HRMS calculated**: $C_{25}H_{22}N_2O_3$ $(M+H)^+$ 399.1709; found 399.1707

3.4b-1): 5-methoxy-3-(1*H*-pyrrol-1-yl)-1-(4-(trifluoromethyl)benzyl)indolin-2-one



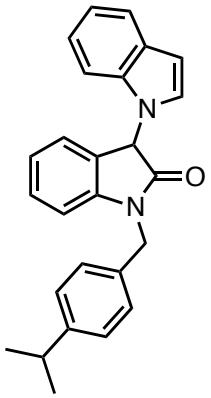
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 6.93 (dd, *J* = 2.6, 1.1 Hz, 1H), 6.84 – 6.78 (m, 1H), 6.71 (t, *J* = 2.1 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 1H), 6.27 (t, *J* = 2.1 Hz, 2H), 5.58 (d, *J* = 1.0 Hz, 1H), 4.95 (q, *J* = 15.9 Hz, 2H), 3.74 (s, 3H)**. ^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.41, 156.63, 139.47, 136.09, 130.22 (q, J_{CF} = 31.9, 31.1 Hz), 127.60, 125.92(q, J_{CF} = 3.7 Hz), 125.66, 123.91 (q, J_{CF} = 272.2 Hz), 120.25, 115.05, 112.39, 110.01, 109.70, 60.63, 55.84, 43.69 **HRMS calculated**: $C_{21}H_{17}F_3N_2O_2$ $(M+H)^+$ 387.1320; found 387.1301

3.2d-1): 5-fluoro-1-(4-methoxybenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one



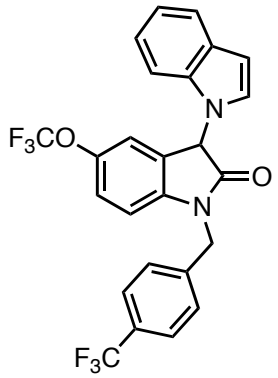
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.95 (ddd, *J* = 7.5, 2.7, 1.2 Hz, 1H), 6.89 (td, *J* = 8.7, 2.4 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.65 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.59 (t, *J* = 2.2 Hz, 2H), 6.18 (t, *J* = 2.2 Hz, 2H), 5.46 (s, 1H), 4.86 – 4.66 (m, 2H), 3.70 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.31, 159.38(d, J_{CF} = 243.66 Hz), 159.32, 139.15, 139.14, 128.79, 127.03, 126.25(d, J_{CF} = 8.2 Hz), 120.22, 116.53(d, J_{CF} = 23.4 Hz), 114.35, 113.42 (d, J_{CF} = 25.1 Hz), 110.47 (d, J_{CF} = 7.9 Hz), 109.82, 60.45, 55.30, 43.74. **HRMS calculated**: $C_{20}H_{17}FN_2O_2$ $(M+H)^+$ 337.1352; found 337.1336

3.1a-4) 3-(1*H*-indol-1-yl)-1-(4-isopropylbenzyl)indolin-2-one ^{1}H NMR



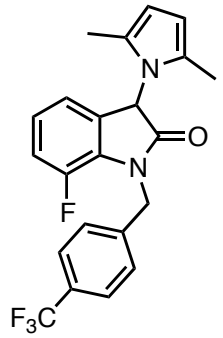
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 1H), 7.33 – 7.28 (m, 3H), 7.22 – 7.18 (m, 2H), 7.16 (dt, *J* = 7.3, 1.3 Hz, 1H), 7.14 – 7.07 (m, 2H), 7.06 – 6.98 (m, 3H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.58 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.94 (s, 1H), 5.07 – 4.84 (m, 2H), 2.90 (hept, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.61, 148.68, 143.11, 136.18, 132.68, 130.03, 129.23, 127.75, 126.95, 125.08, 124.67, 123.26, 122.09, 121.21, 120.09, 109.83, 103.09, 58.56, 44.03, 33.80, 23.94, 0.00. **HRMS calculated**: $C_{26}H_{24}N_2O$ $(M+H)^+$ 381.1967; found 381.1958

3.4f-4) : 3-(1*H*-indol-1-yl)-5-(trifluoromethoxy)-1-(4- (trifluoromethyl) benzyl)indolin-2-one



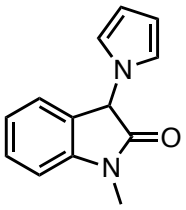
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.65 (m, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.08 (m, 3H), 7.02 (d, *J* = 3.3 Hz, 1H), 6.99 – 6.91 (m, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.63 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.99 (s, 1H), 5.16 – 4.93 (m, 2H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.49, 145.37, 141.16, 138.88, 136.08, 130.63 (q, J_{CF} = 32.8 Hz), 129.32, 127.96, 126.11 (q, J_{CF} = 3.6 Hz), 126.04, 126.00 (q, J_{CF} = 272.06 Hz) 123.38, 122.44, 121.51, 120.50, 119.41, 110.09, 109.41, 103.85, 58.40, 41.01. **HRMS calculated**: $C_{25}H_{16}F_6N_2O_2$ $(M+H)^+$ 491.1194; found 491.1176

3.4e-2): 3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-1-(4-(trifluoromethyl) benzyl)indolin-2-one



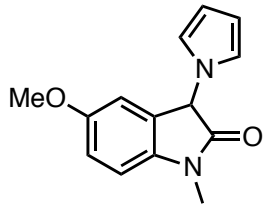
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 4H), 7.10 – 7.04 (m, 1H), 7.01 (ddd, *J* = 8.5, 7.3, 4.5 Hz, 1H), 6.90 (dt, *J* = 7.3, 1.2 Hz, 1H), 5.87 (dd, *J* = 3.4, 1.1 Hz, 1H), 5.77 (dd, *J* = 3.2, 1.1 Hz, 1H), 5.67 (s, 1H), 5.23 – 5.07 (m, 2H), 2.40 (s, 3H), 1.52 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.95, 147.39 (d, J_{CF} = 244.5 Hz), 140.38, 129.35, 128.51 (d, J_{CF} = 1.8 Hz), 127.60, 125.66 (q, J_{CF} = 3.6 Hz), 124.30 (d, J_{CF} = 6.4 Hz), 120.32 (d, J_{CF} = 3.2 Hz), 117.72 (d, J_{CF} = 19.6 Hz), 107.63, 106.57, 56.81, 45.53, 41.03, 12.88, 12.41. **HRMS calculated**: $C_{22}H_{18}F_4N_2O$ $(M+H)^+$ 403.1434; found 403.1448

3.5a-1): 1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one



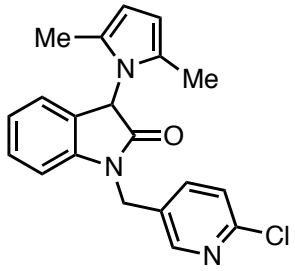
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (tt, *J* = 7.7, 1.0 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.11 (td, *J* = 7.5, 0.9 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.69 (t, *J* = 2.1 Hz, 2H), 6.23 (t, *J* = 2.1 Hz, 2H), 5.49 (s, 1H), 3.24 (s, 3H**). ^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.48, 144.20, 130.21, 125.34, 124.53, 123.25, 120.24, 109.39, 108.66, 60.31, 26.53.. **HRMS calculated**: $C_{13}H_{12}N_2O$ $(M+H)^+$ 213.1028; found 213.1057

3.5d-1): 5-methoxy-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one



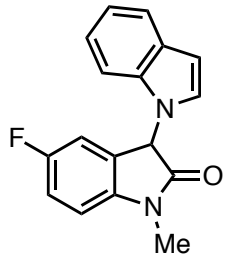
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 – 6.89 (m, 2H), 6.86 – 6.75 (m, 1H), 6.69 (t, *J* = 2.1 Hz, 2H), 6.23 (t, *J* = 2.2 Hz, 2H), 5.45 (s, 1H), 3.77 (s, 3H), 3.21 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.14, 156.43, 137.55, 125.65, 120.27, 114.95, 112.16, 109.41, 109.15, 60.66, 55.87, 26.60. **HRMS calculated**: $C_{14}H_{14}N_2O_2$ $(M+H)^+$ 243.1134; found 243.1162

3.3a-2): 1-((6-Chloropyridin-3-yl)methyl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)indolin-2-one



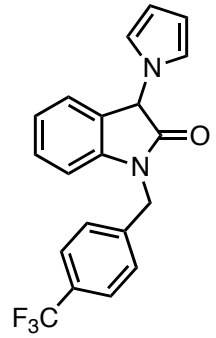
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.6 Hz, 1H), 7.72 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.14 – 7.04 (m, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.88 (dd, *J* = 3.3, 1.0 Hz, 1H), 5.77 (dd, *J* = 3.3, 1.2 Hz, 1H), 5.69 (s, 1H), 5.01 – 4.90 (m, 3H), 2.62 (s, 6H**).** **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.37, 151.36, 149.06, 141.53, 138.63, 130.28, 129.63, 129.42, 127.55, 125.68, 124.63, 123.79, 108.91, 107.53, 106.45, 56.73, 41.11, 12.92, 12.49 **HRMS calculated**: $C_{20}H_{18}ClN_3O$ $(M+H)^+$ 352.1217; found 352.1235

3.3a-2): 1-((6-Chloropyridin-3-yl)methyl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)indolin-2-one



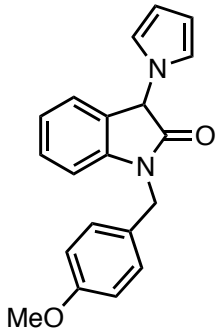
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 1H), 7.17 – 7.08 (m, 3H), 7.06 – 7.02 (m, 1H), 7.00 (d, *J* = 3.3 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.59 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.86 (s, 1H), 3.32 (s, 3H**). ^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.16, 159.48 (d, J_{CF} = 243.0 Hz), 139.75, 136.10, 129.21, 126.87, 126.20 (d, J_{CF} = 8.1 Hz), 122.33, 121.35, 120.26, 116.54 (d, J_{CF} = 23.6 Hz), 113.19 (d, J_{CF} = 25.3 Hz), 109.41, 103.43, 58.53, 26.79. **HRMS calculated**: $C_{17}H_{13}FN_2O$ $(M+H)^+$ 281.1090; found 281.1072

3.4a-1): 3-(1*H*-pyrrol-1-yl)-1-(4-(trifluoromethyl)benzyl)indolin-2-one



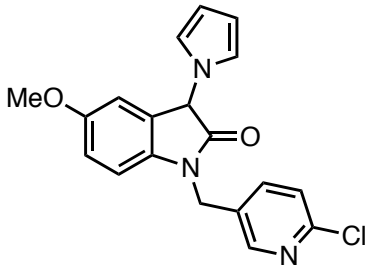
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.74 (t, *J* = 2.1 Hz, 2H), 6.30 (t, *J* = 2.1 Hz, 2H), 5.64 (s, 1H), 5.10 – 4.84 (m, 2H**). ^{13}C NMR (125 MHz,** $CDCl_3$) δ 172.72, 142.90, 139.42, 130.27, 130.25 (q, *J* = 32.6 Hz), 127.65, 125.96 (q, *J* = 3.6 Hz), 125.70, 124.55, 123.95 (d, *J* = 273.13 Hz), 123.65, 109.69, 109.46, 60.29, 43.62. **HRMS calculated**: $C_{20}H_{15}F_3N_2O$ $(M+H)^+$ 357.1215; found 357.1209

3.5a-1): 1-(4-methoxybenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one

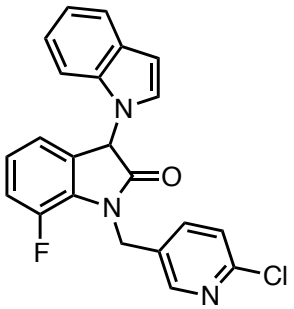


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 4H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.82 – 6.69 (m, 3H), 6.61 (t, *J* = 2.1 Hz, 2H), 6.16 (t, *J* = 2.1 Hz, 2H), 5.46 (s, 1H), 4.82 – 4.68 (m, 2H), 3.68 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.61, 159.24, 143.33, 130.10, 128.85, 127.41, 125.40, 124.69, 123.25, 120.27, 114.28, 109.77, 109.51, 60.39, 55.30, 43.58. **HRMS calculated**: $C_{20}H_{18}N_2O_2$ $(M+H)^+$ 319.1447; found 319.1463

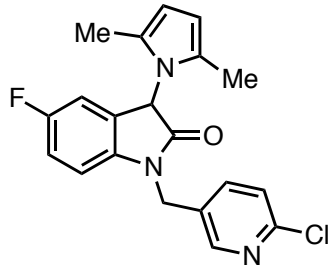
3.3b-1)-((6-Chloropyridin-3-yl)methyl)-5-methoxy-3-(1*H*-pyrrol-1-yl)indolin-2-one



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.5 Hz, 1H), 7.60 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 2.6, 1.2 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.71 – 6.68 (m, 3H), 6.28 (t, *J* = 2.2 Hz, 2H), 5.57 (d, *J* = 1.0 Hz, 1H), 4.97 – 4.82 (m, 2H), 3.76 (s, 3H**). ^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.47, 156.77, 151.30, 148.77, 138.15, 135.63, 130.28, 125.66, 124.74, 120.22, 115.07, 112.61, 109.78, 60.54, 55.87
HRMS calculated: $C_{19}H_{16}ClN_3O_2$ $(M+H)^+$ 354.1009; found 354.0993

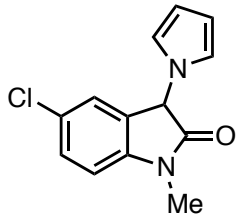


3.3e-4): 1-((6-Chloropyridin-3-yl)methyl)-7-fluoro-3-(1*H*-indol-1-yl)indolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (t, *J* = 2.1 Hz, 1H), 7.72 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.64 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.06 (m, 3H), 7.04 – 6.97 (m, 3H), 6.88 (s, 1H), 6.60 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.93 (s, 1H), 5.24 – 4.99 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.50, 151.40, 149.49, 147.47 (d, J_{CF} = 244.6 Hz), 139.02, 135.96, 131.13, 129.30, 128.83 (d, J_{CF} = 9.0 Hz), 127.25 (d, J_{CF} = 2.8 Hz), 126.90, 124.66 (J_{CF}, *J* = 6.5 Hz), 124.49, 122.36, 121.46,121.35 (d, J_{CF} = 3.4 Hz), 120.43, 118.38 (d, J_{CF} = 19.3 Hz), 109.42, 103.65, 58.52, 42.81. **HRMS calculated**: $C_{22}H_{15}ClFN_3O$ $(M+H)^+$ 392.0966; found 392.0959



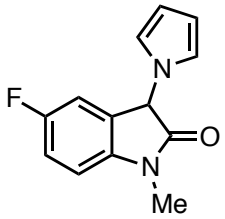
3.3d-2): 1-((6-Chloropyridin-3-yl)methyl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoroindolin-2-one ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.01 (td, *J* = 8.9, 2.8 Hz, 1H), 6.88 (ddd, *J* = 7.3, 2.6, 1.3 Hz, 1H), 6.76 (dd, *J* = 8.6, 3.9 Hz, 1H), 5.88 (d, *J* = 3.3 Hz, 1H), 5.79 (dd, *J* = 3.5, 1.2 Hz, 1H), 5.67 (s, 1H), 5.01 – 4.89 (m, 2H), 2.40 (s, 3H), 1.56 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 173.08, 159.75 (d, J_{CF} = 243.9 Hz), 151.53, 148.98, 138.55, 159.75 (d, J_{CF} = 243.9 Hz), 129.99, 129.33, 127.41, 127.36 (d, J_{CF} = 8.3 Hz), 124.71, 116.06 (d, J_{CF} = 23.6 Hz), 112.83 (d, J_{CF} = 25.3 Hz), 109.62 (d, J_{CF} = 8.1 Hz), 107.84, 106.75, 56.79, 41.29, 12.88, 12.52. **HRMS calculated**: $C_{20}H_{17}ClFN_3O$ $(M+H)^+$ 370.1122; found 370.1109

3.5c-1): 5-Chloro-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1H), 7.31 – 7.26 (m, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.66 (t, *J* = 2.1 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 5.48 (s, 1H), 3.23 (s, 3H). ^{13}C NMR **(125 MHz, $CDCl_3$)** δ 171.98, 142.64, 130.19, 128.76, 126.20, 125.71, 120.21, 109.75, 109.64, 60.15, 26.68. **HRMS calculated**: $C_{13}H_{11}ClN_2O$ $(M+H)^+$ 247.0638; found 247.0672.

3.5d-1): 5-fluoro-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one

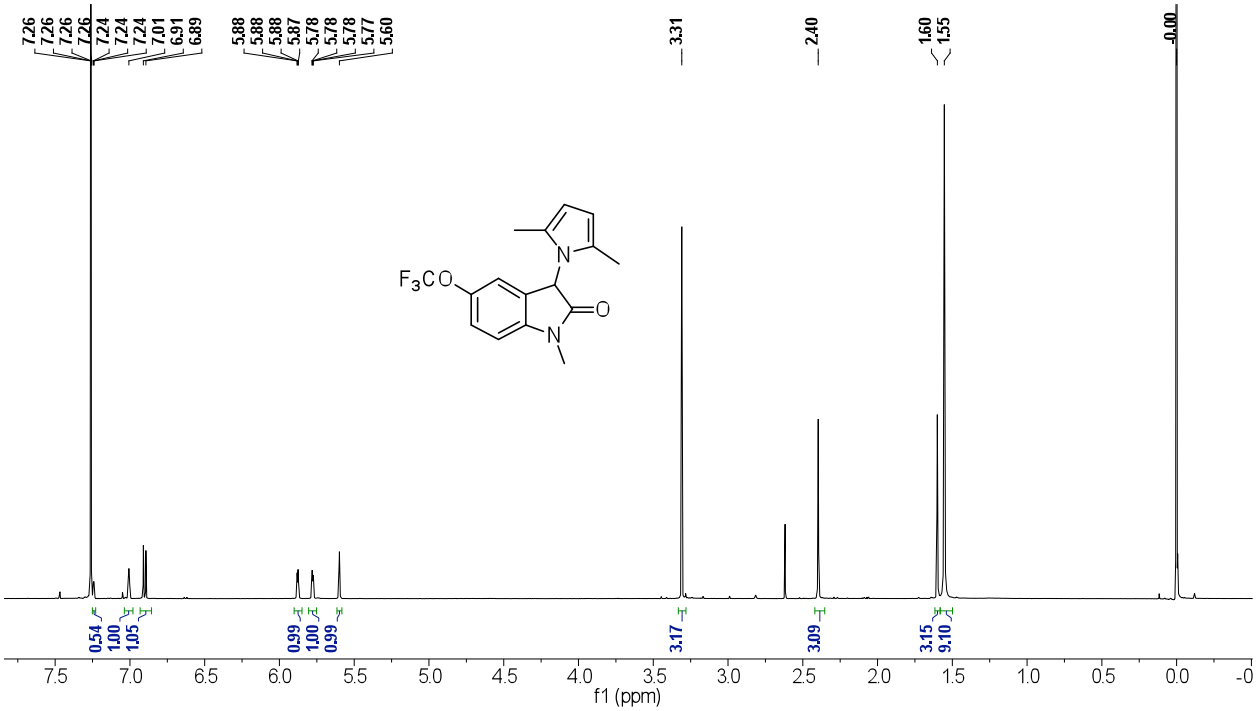


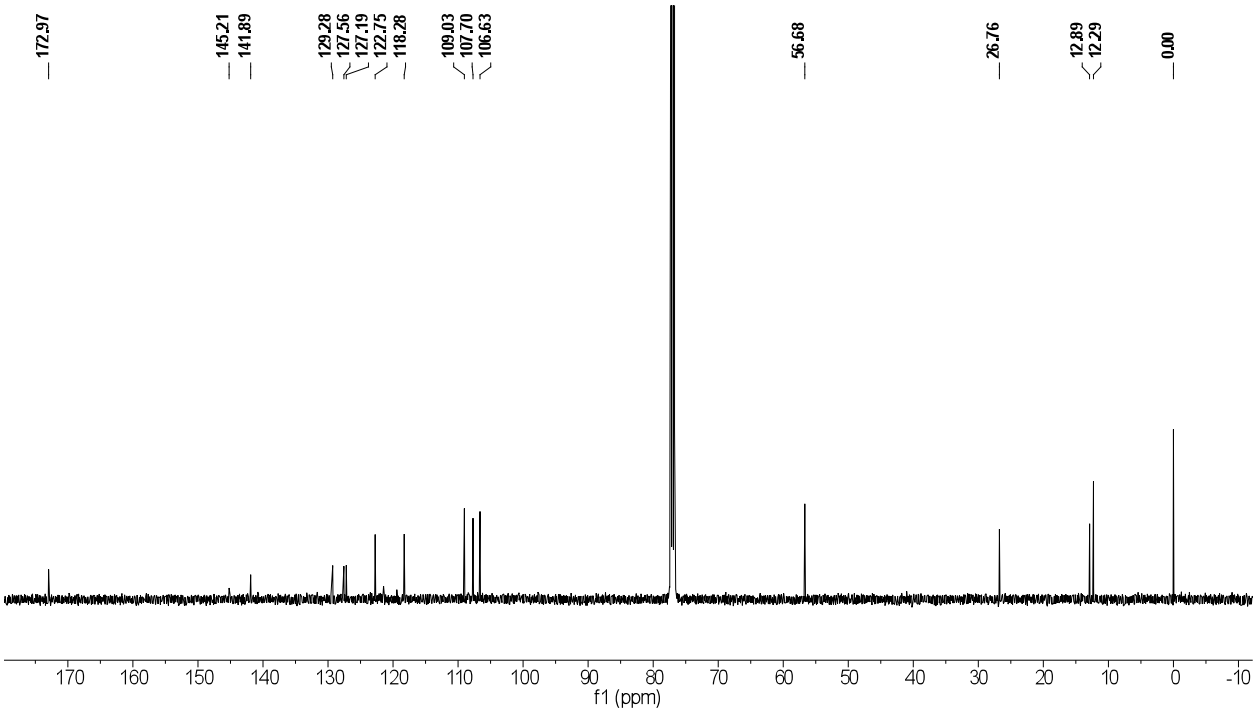
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.07 (m, 1H), 7.06 (ddd, *J* = 7.6, 2.7, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.67 (t, *J* = 2.1 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 5.48 (d, *J* = 1.2 Hz, 1H), 3.24 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 172.14, 159.44 (d, *J* = 242.5 Hz), 140.08 (d, *J* = 1.7 Hz), 126.08 (d, *J* = 8.2 Hz), 120.20, 116.59 (d, J_{CF} = 23.4 Hz), 113.46 (d, *J* = 25.1 Hz), 109.71, 109.29 (d, *J* = 8.1 Hz), 60.41, 26.70. **HRMS calculated**: $C_{13}H_{11}FN_2O$ $(M+H)^+$ 231.0934; found 231.0957.

Spectra for Oxindoles

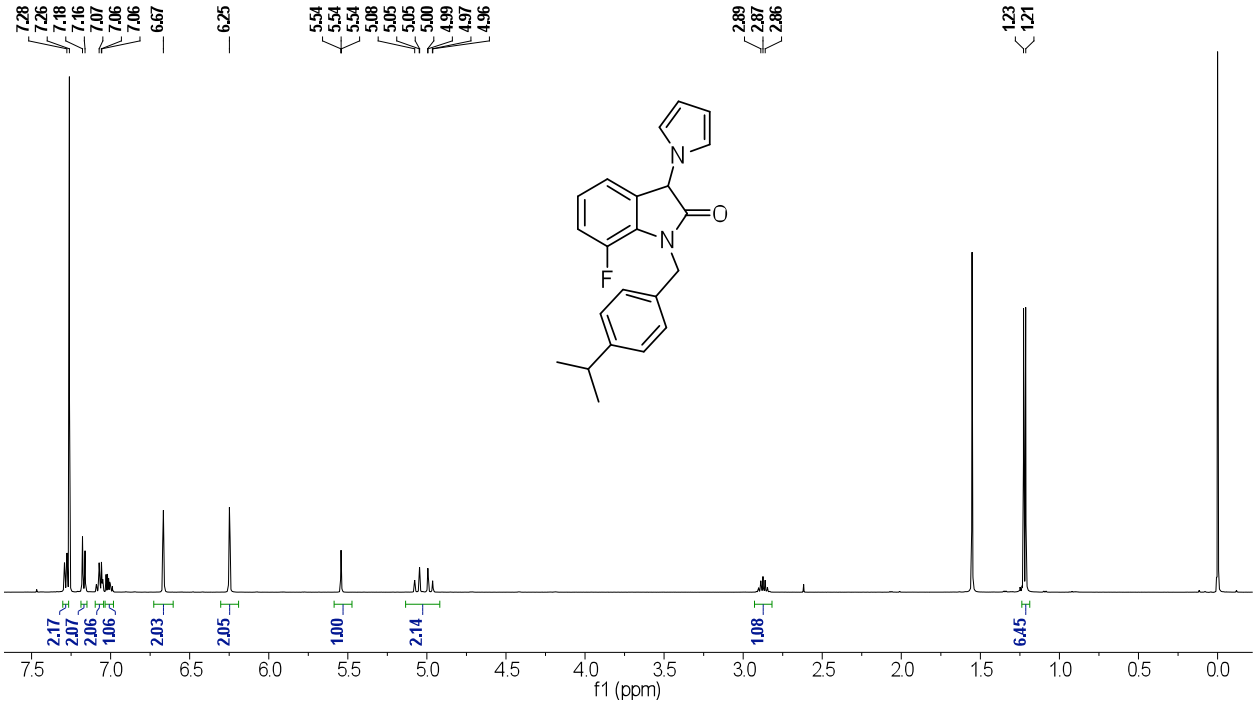
Copies of selected ^{1}H and ^{13}C NMR spectra

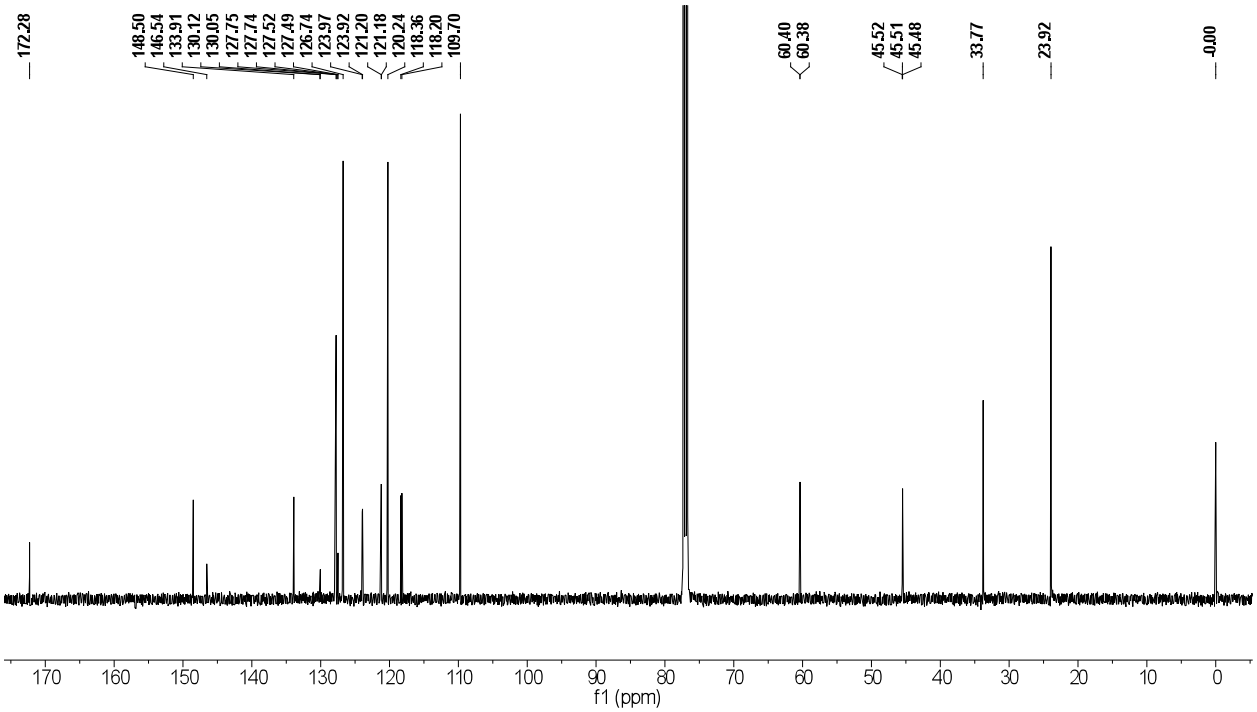
3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-1-methyl-5-(trifluoromethoxy)indolin-2-one (3.5f-2)



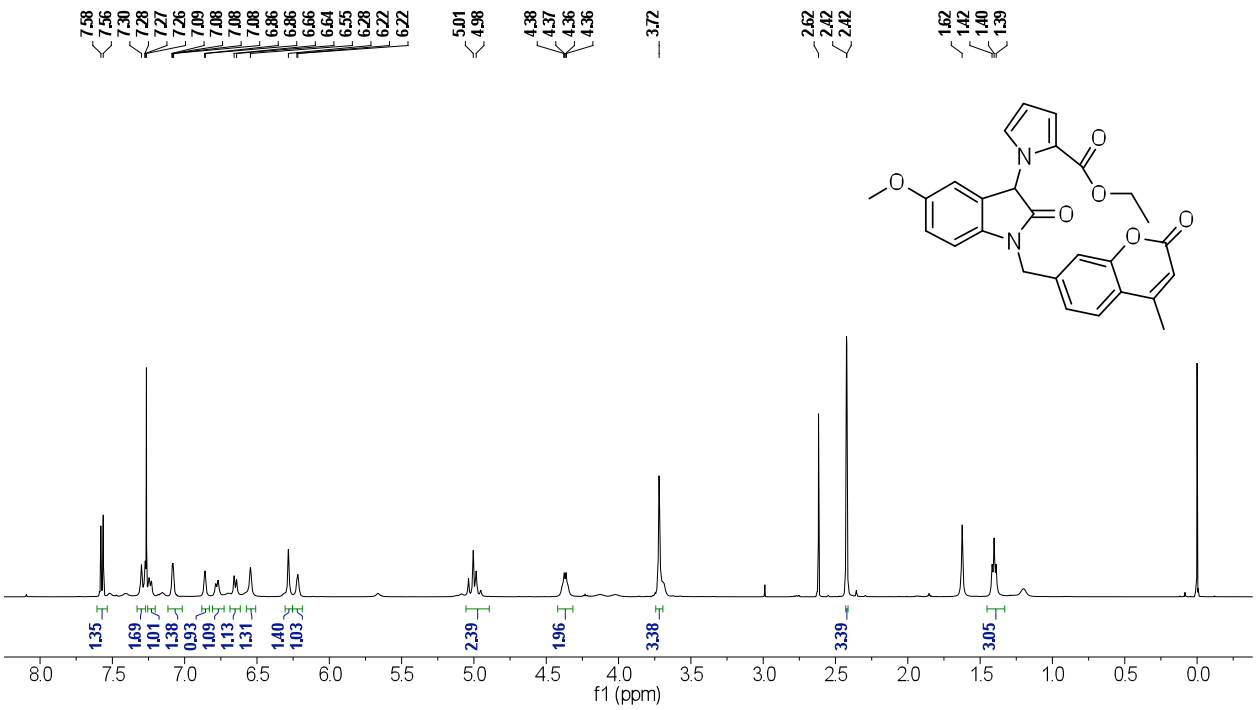


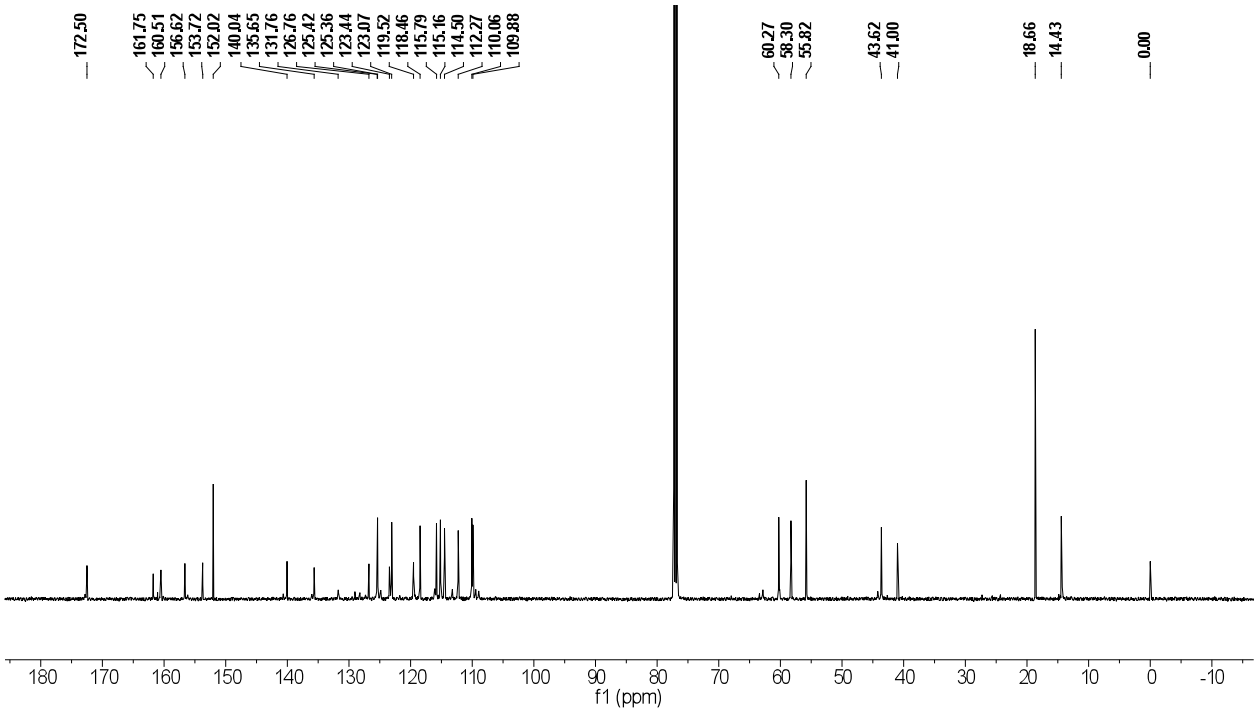
7-fluoro-1-(4-isopropylbenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.1e-1)



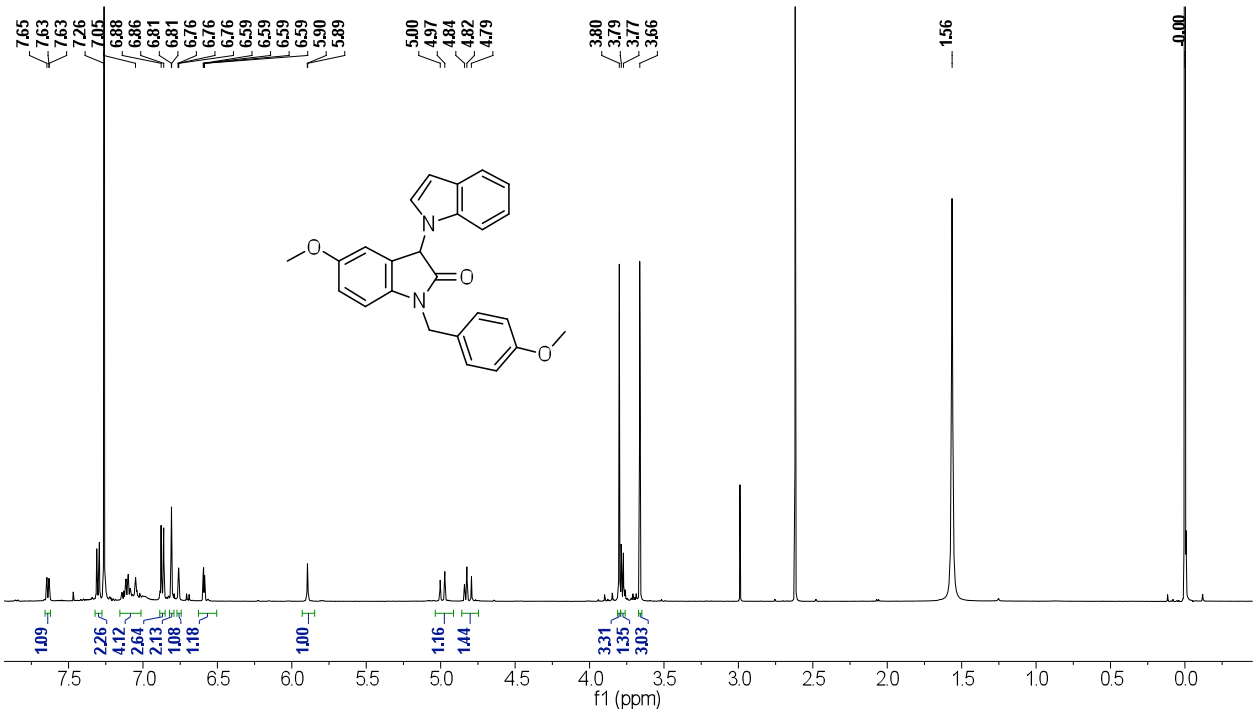


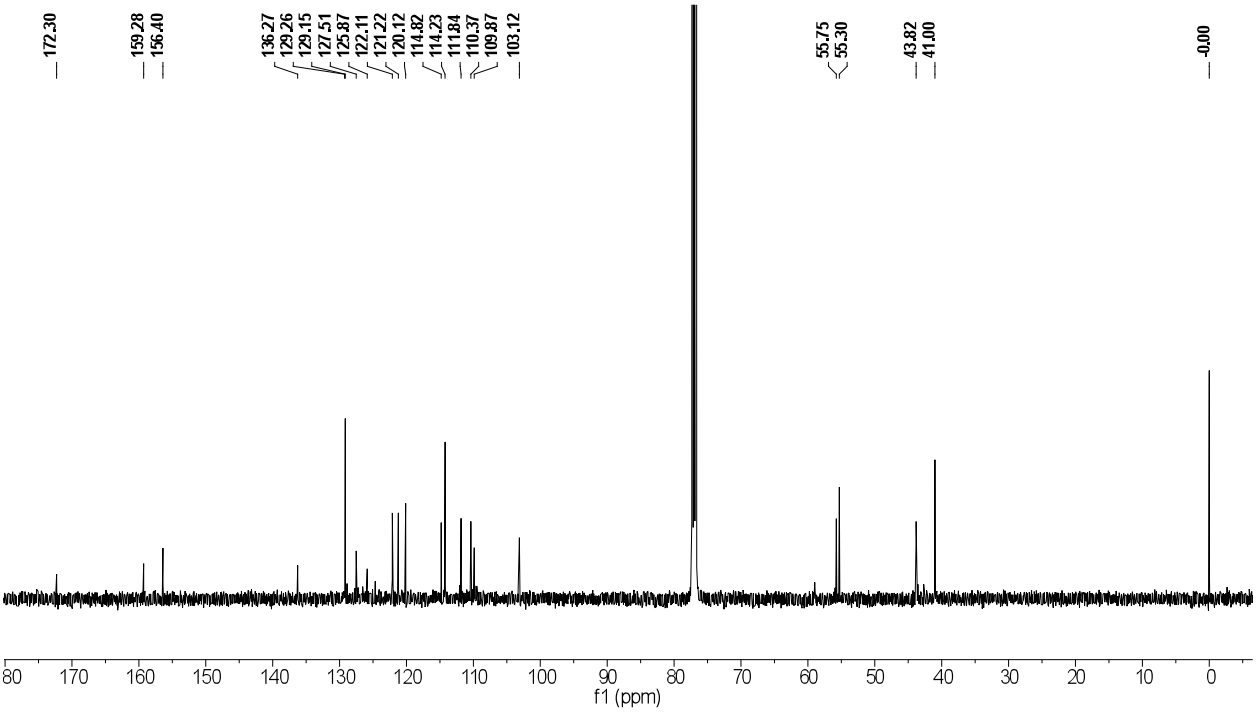
Ethyl 1-(5-methoxy-1-((4-methyl-2-oxo-2*H*-chromen-7-yl)methyl)-2-oxoindolin-3-yl)-1*H*-pyrrole-2-carboxylate (3.6b-3)



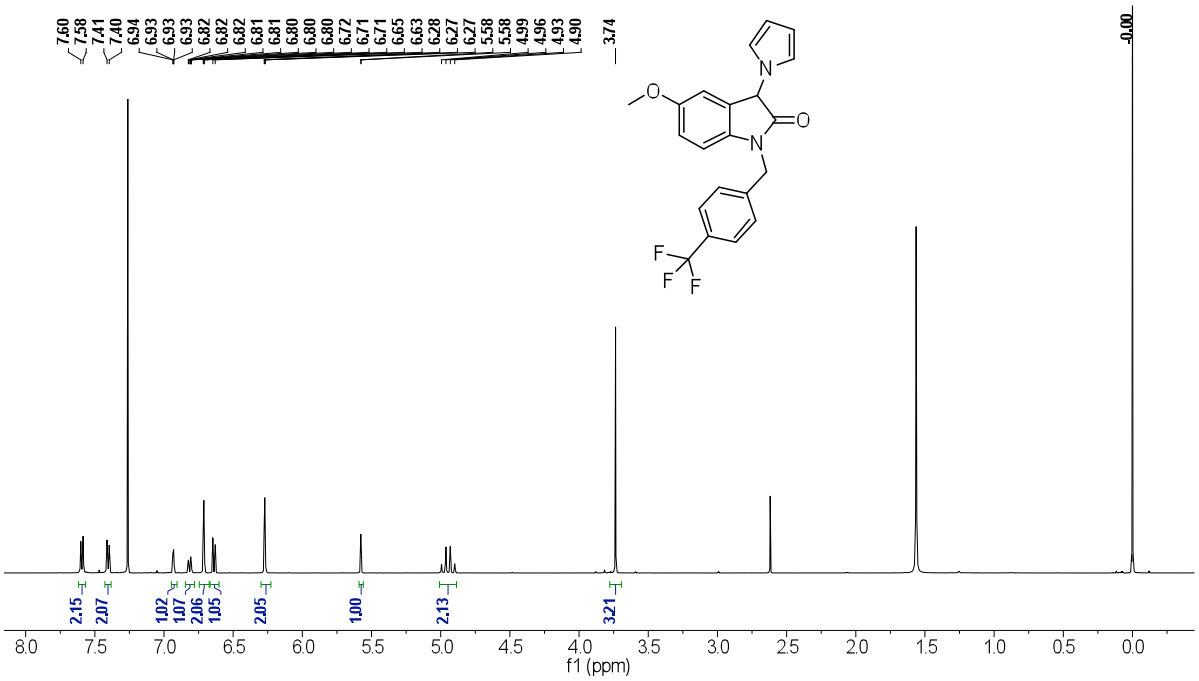

172.50
161.75
160.51
156.62
153.72
152.02
140.04
135.65
131.76
126.76
125.42
125.36
123.44
123.07
119.52
118.46
115.79
115.16
114.50
112.27
110.06
109.88
60.27
58.30
55.82
43.62
41.00
18.66
14.43
0.00
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

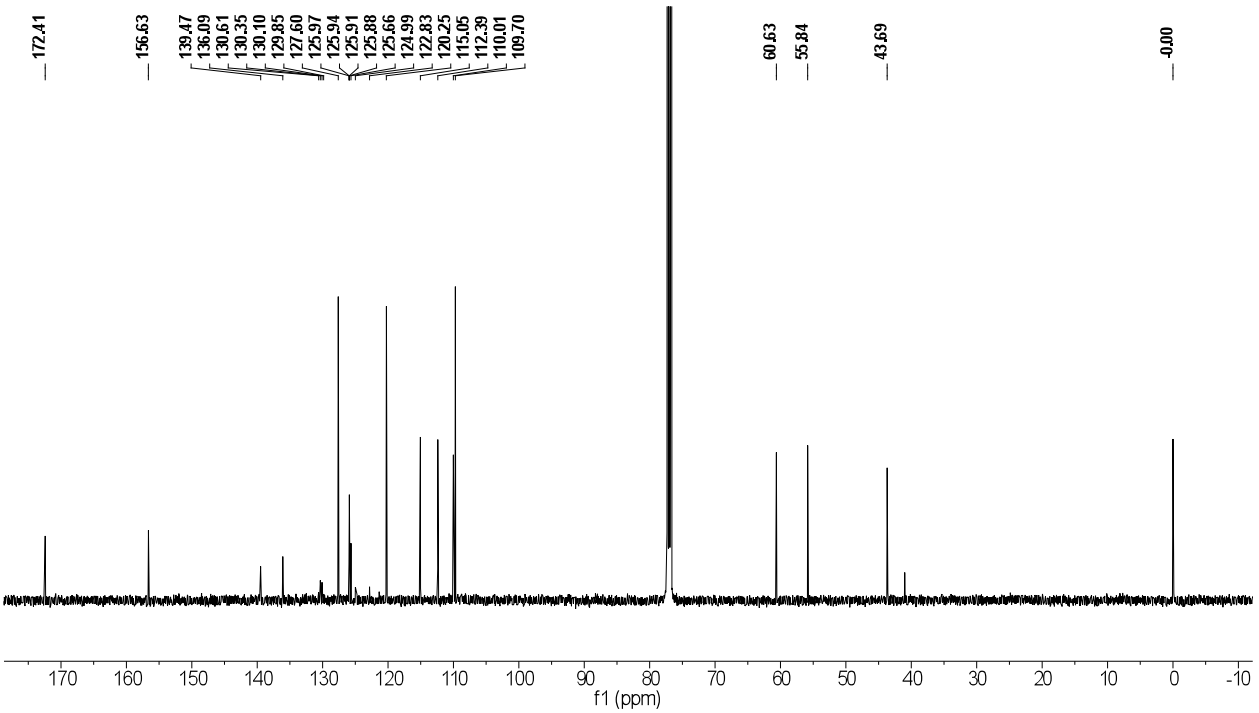
3-(1*H*-indol-1-yl)-5-methoxy-1-(4-methoxybenzyl)indolin-2-one (3.2b-4)



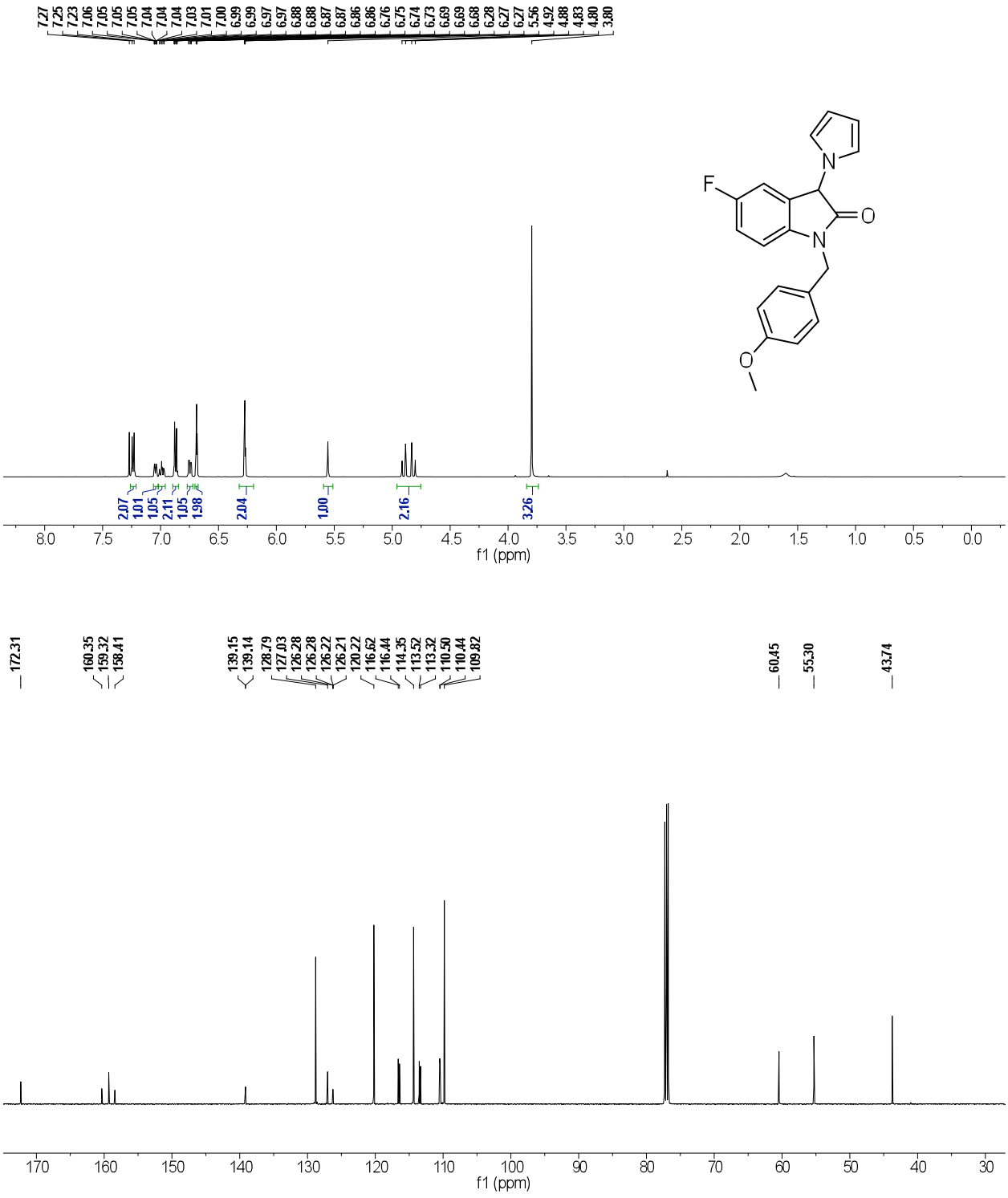


5-methoxy-3-(1*H*-pyrrol-1-yl)-1-(4-(trifluoromethyl)benzyl)indolin-2-one (3.4b-1)

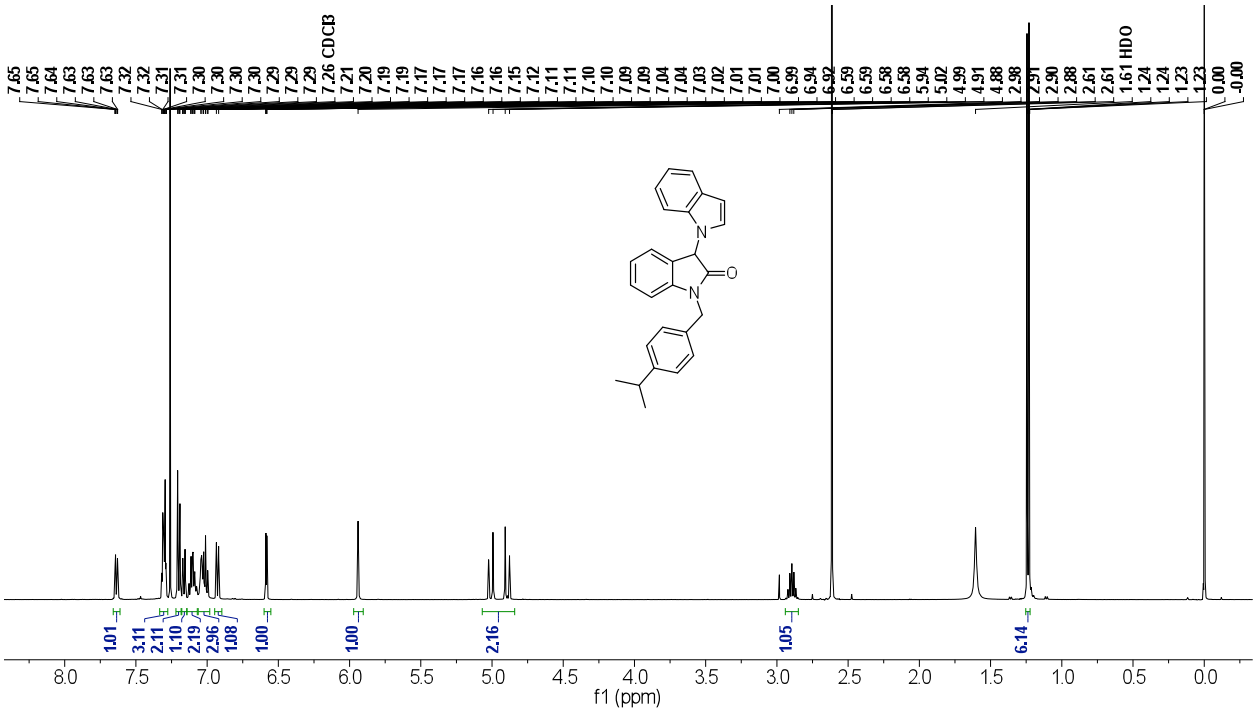


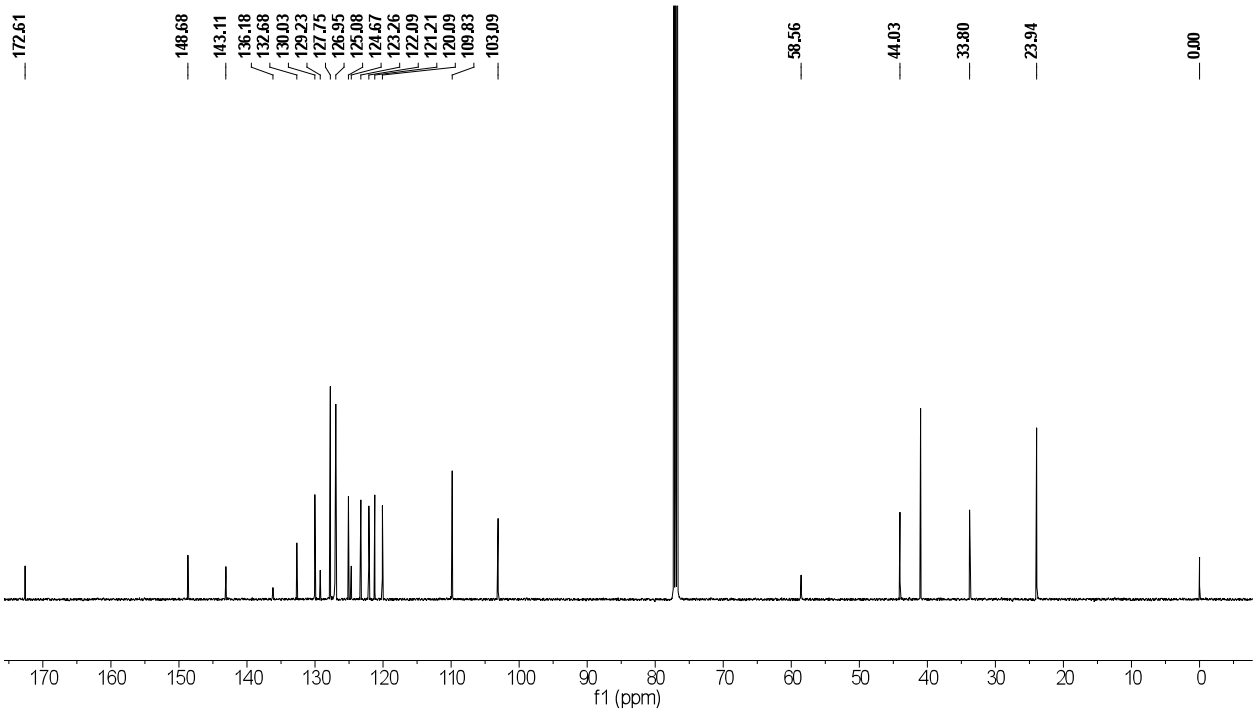


5-fluoro-1-(4-methoxybenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.2d-1)

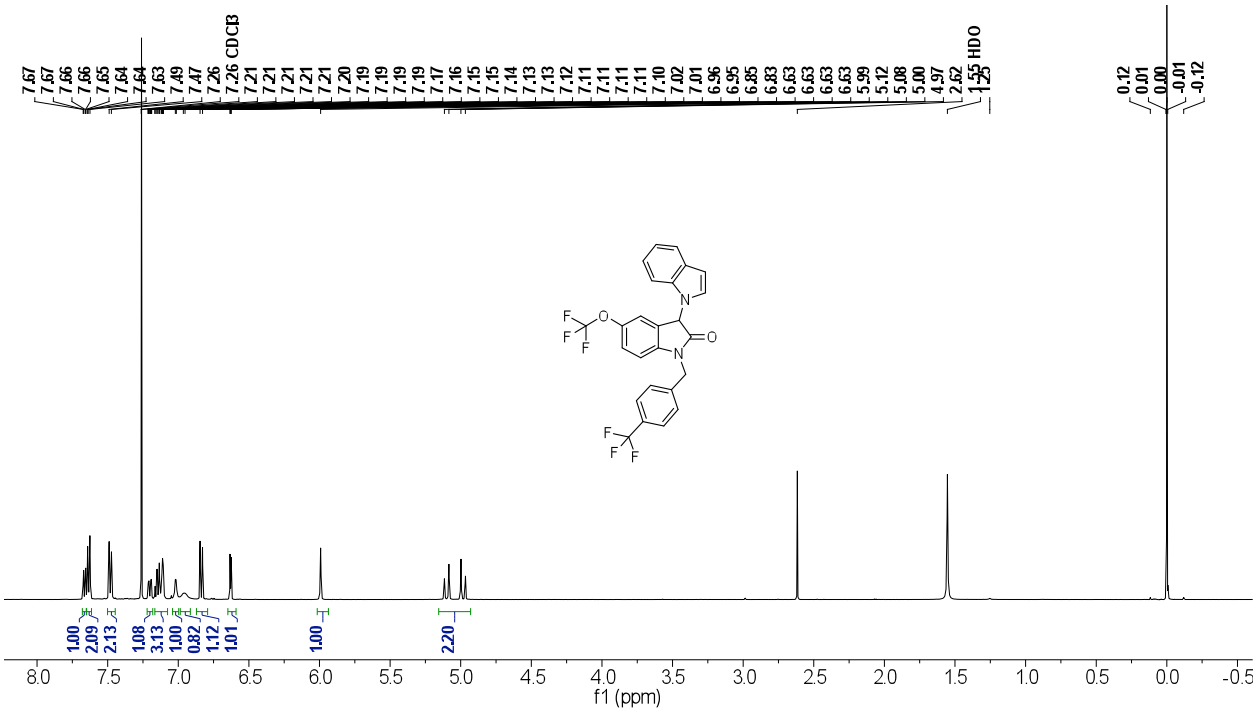


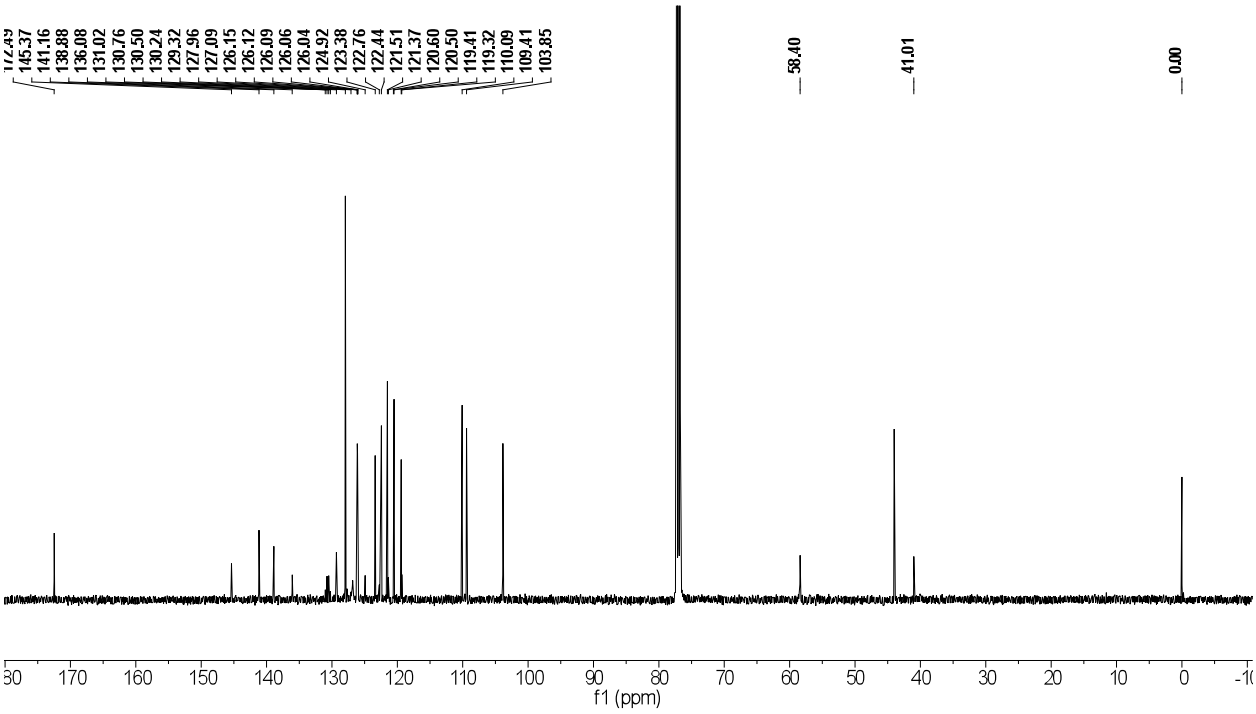
3-(1*H*-indol-1-yl)-1-(4-isopropylbenzyl)indolin-2-one (3.1a-4)



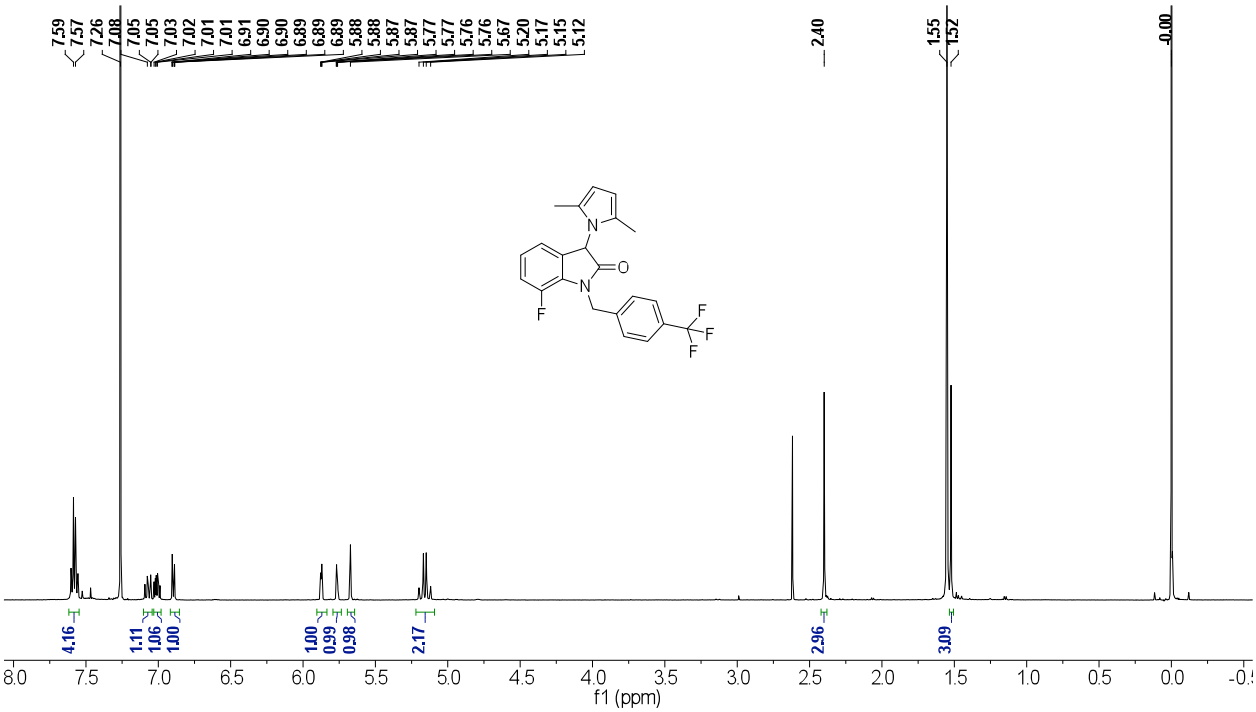


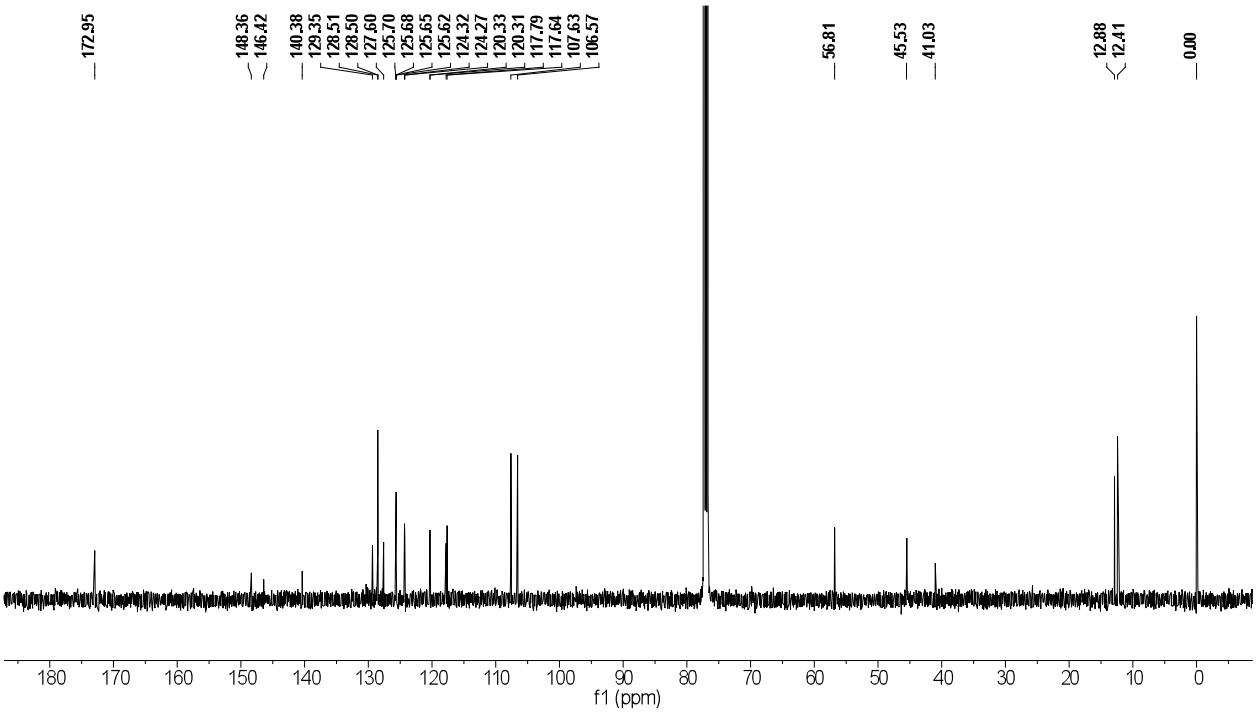
3-(1*H*-indol-1-yl)-5-(trifluoromethoxy)-1-(4-(trifluoromethyl)benzyl)indolin-2-one (3.4f-4)


7.67
7.67
7.66
7.66
7.65
7.64
7.64
7.63
7.49
7.47
7.26
7.26 CDCl3
7.21
7.21
7.21
7.21
7.21
7.20
7.19
7.19
7.19
7.19
7.17
7.16
7.15
7.15
7.14
7.13
7.13
7.12
7.11
7.11
7.11
7.11
7.10
7.02
7.01
6.96
6.95
6.85
6.83
6.63
6.63
6.63
6.63
5.99
5.12
5.08
5.00
4.97
2.62
1.55 H2O
1.25
0.12
0.01
0.00
-0.01
-0.12
1.00
2.09
2.13
1.08
3.13
1.00
0.82
1.12
1.01
1.00
2.20
F
F
F
O
N
O
N
F
F
F
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

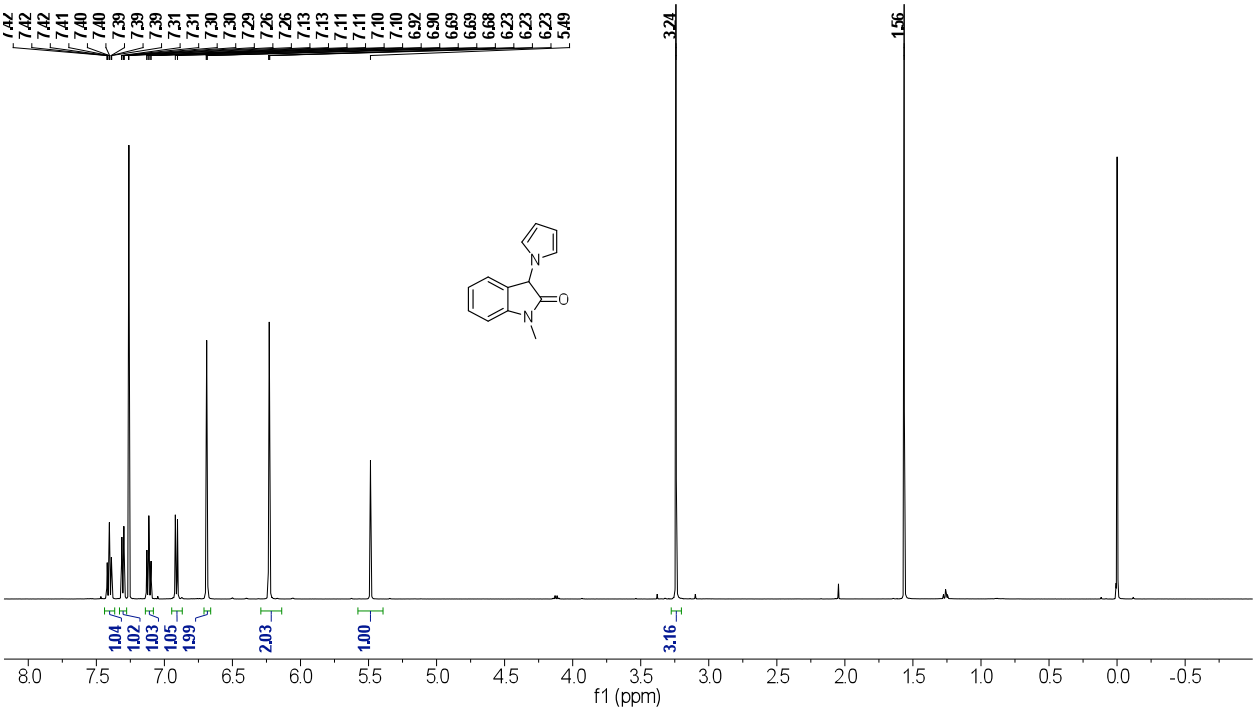

172.49
145.37
141.16
138.88
136.08
131.02
130.76
130.50
130.24
129.32
127.96
127.09
126.15
126.12
126.09
126.06
126.04
124.92
123.38
122.76
122.44
121.51
121.37
120.60
120.50
119.41
119.32
110.09
109.41
103.85
58.40
41.01
0.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

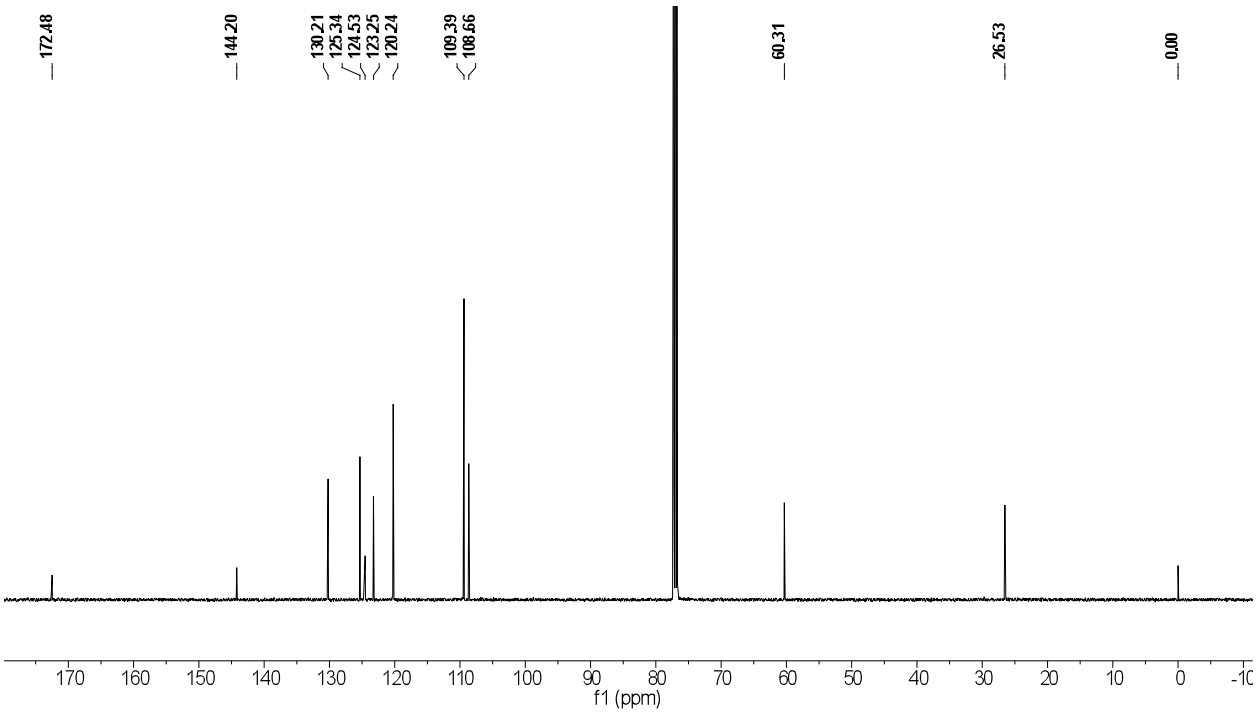
3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-1-(4-(trifluoromethyl)benzyl)indolin-2-one (3.4e-2)



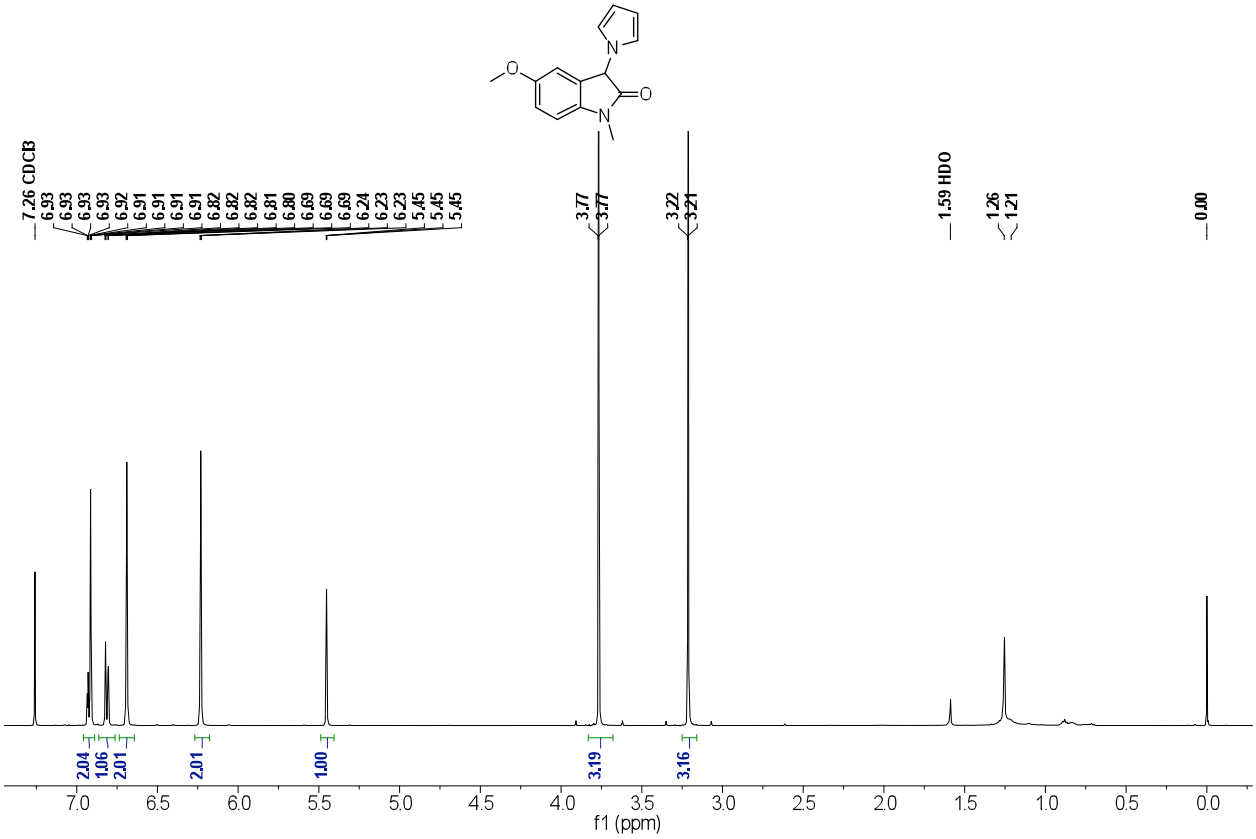


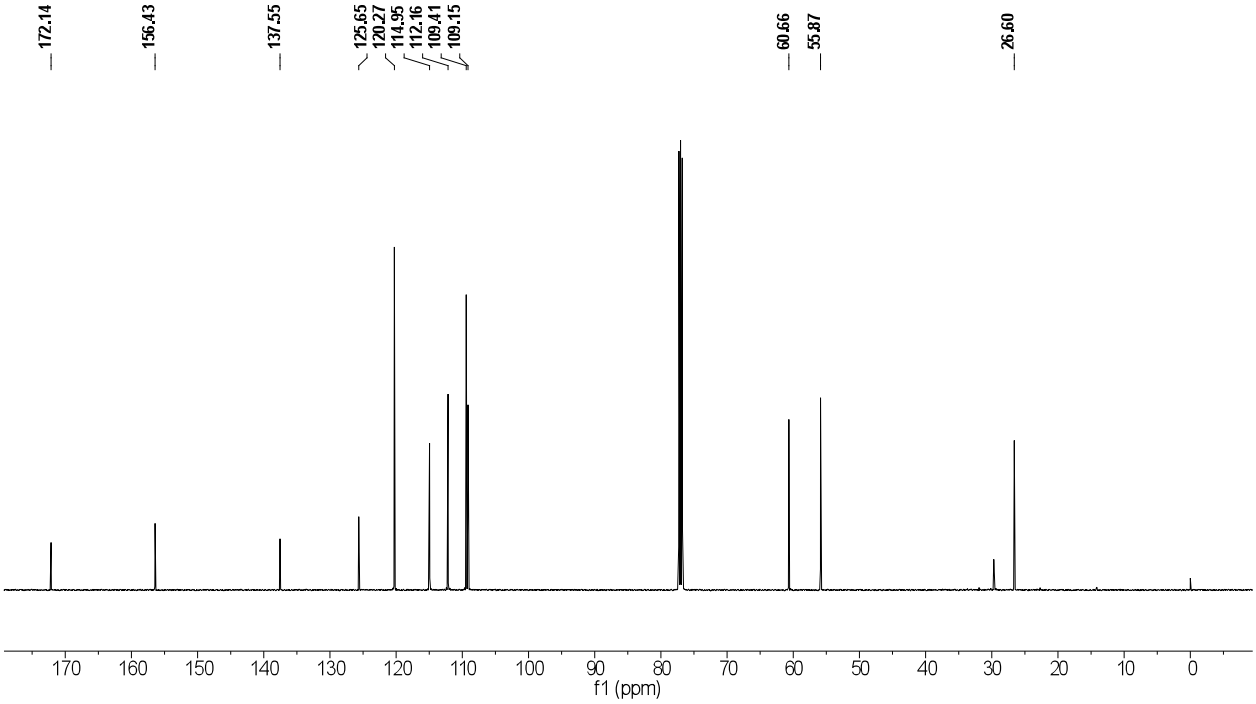
1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.5a-1)



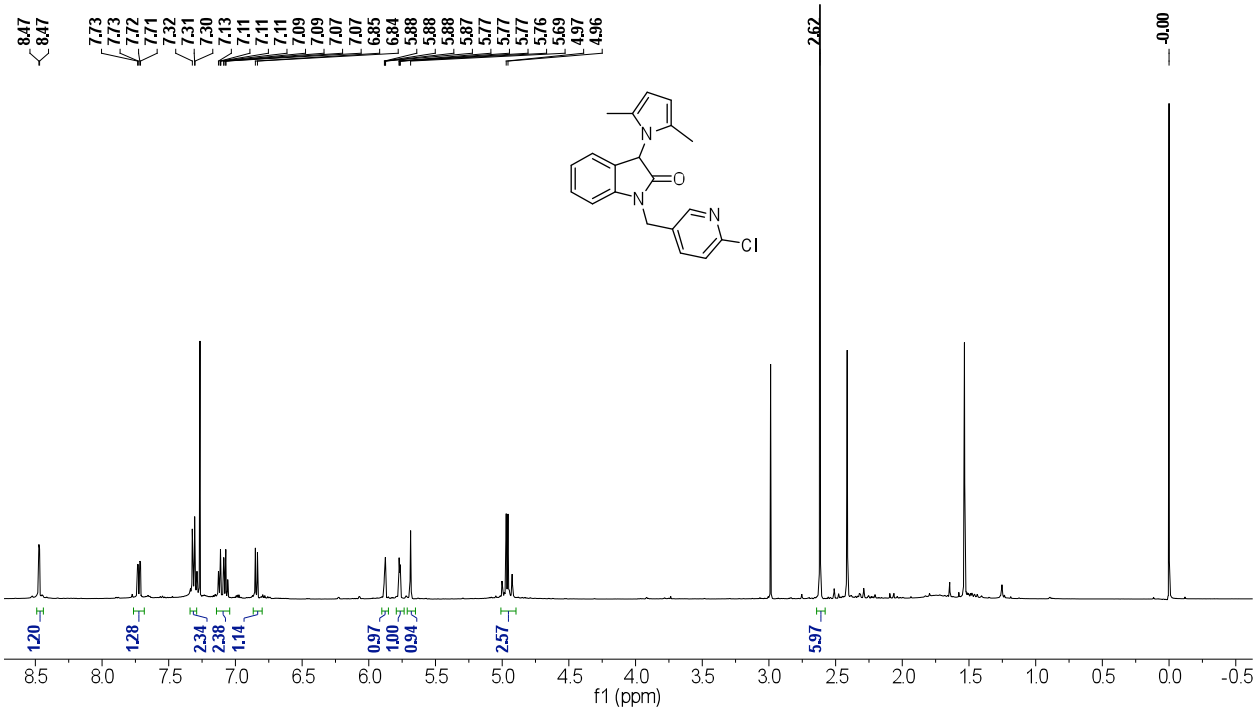


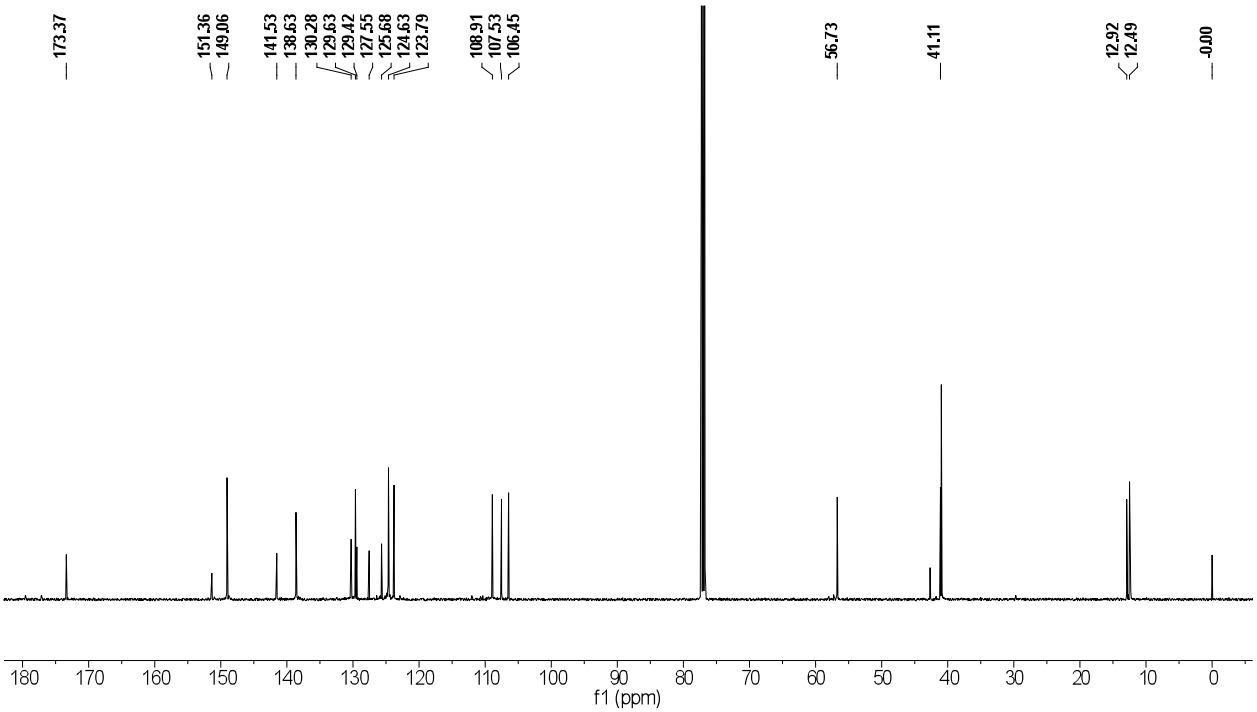
5-methoxy-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.5d.-1)



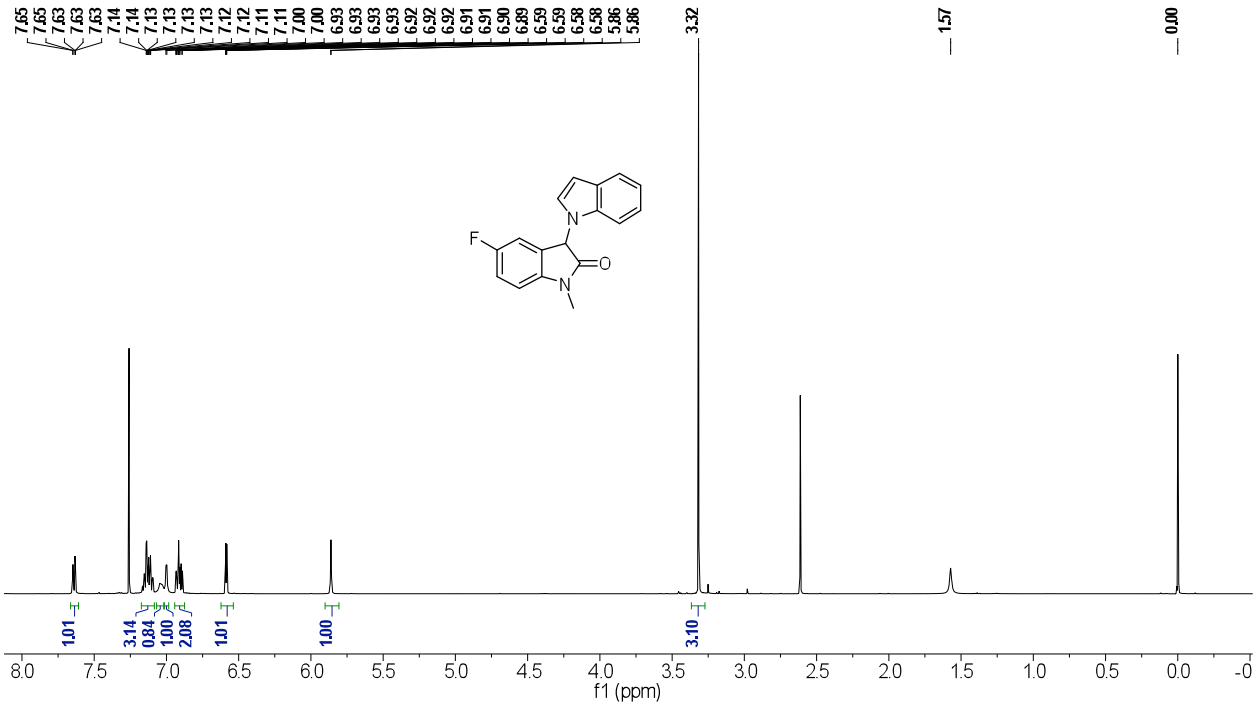


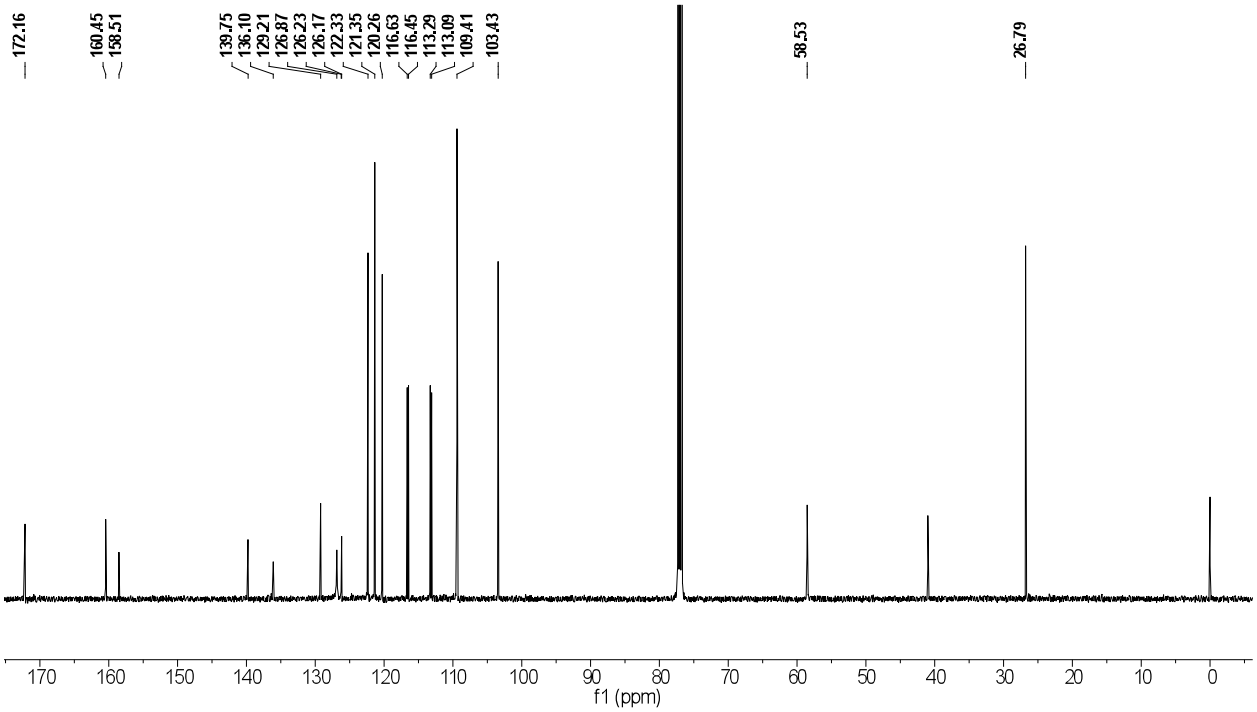
1-((6-chloropyridin-3-yl)methyl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)indolin-2-one (3.3a-2)



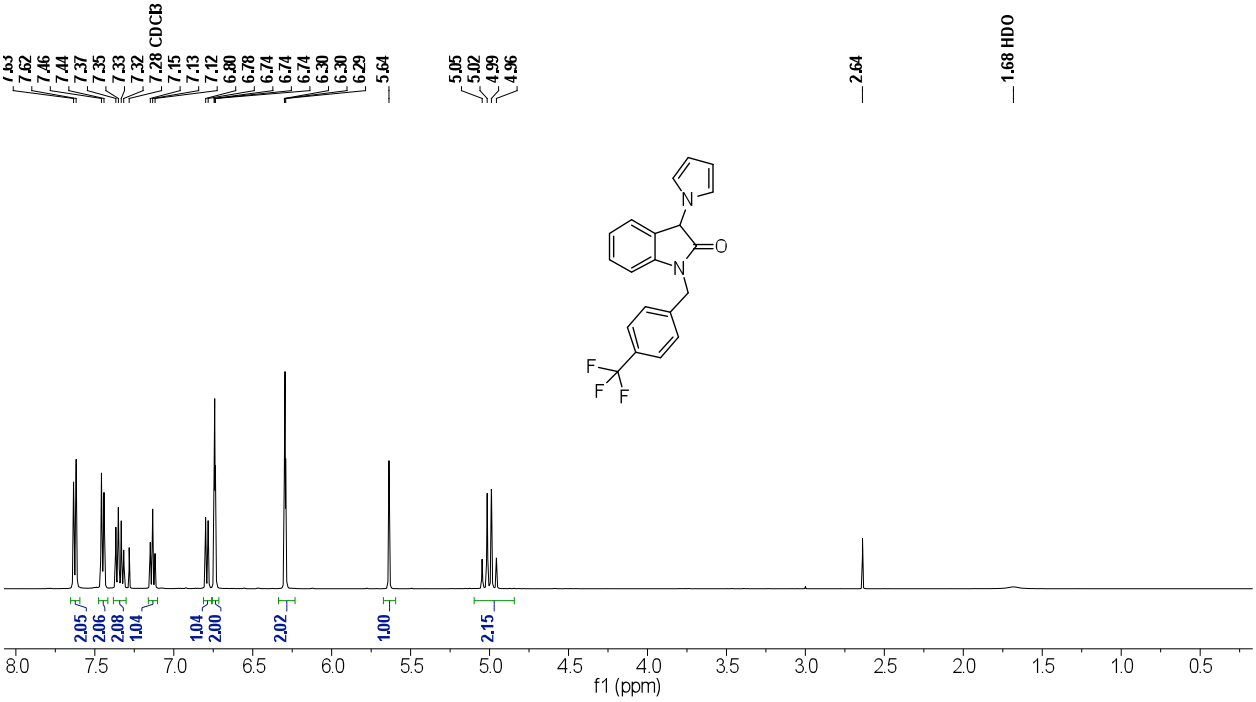


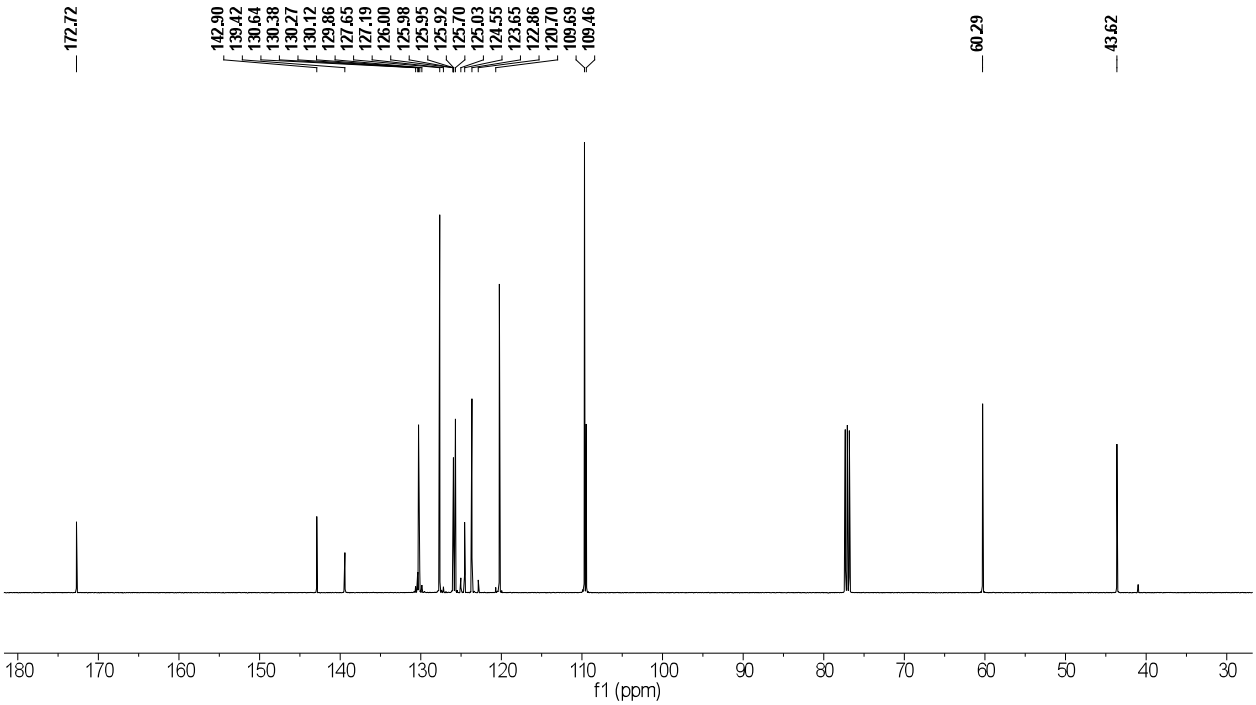
5-fluoro-3-(1*H*-indol-1-yl)-1-methylindolin-2-one (3.5d-4)



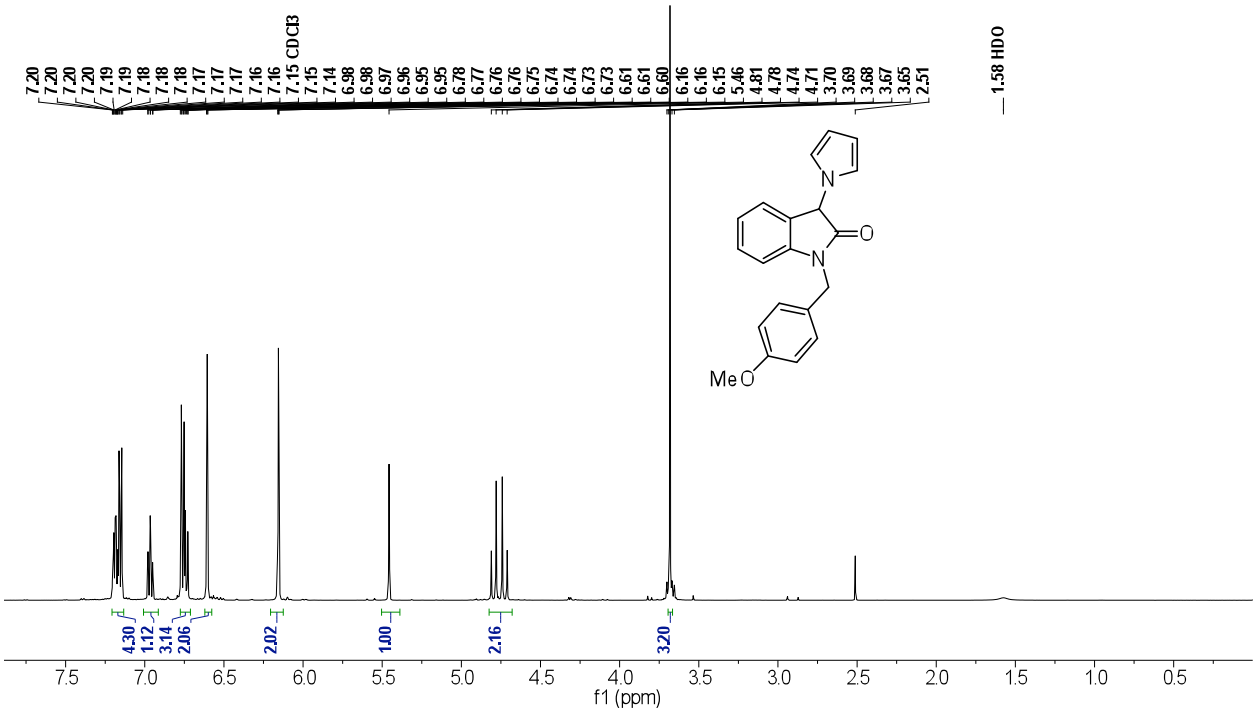


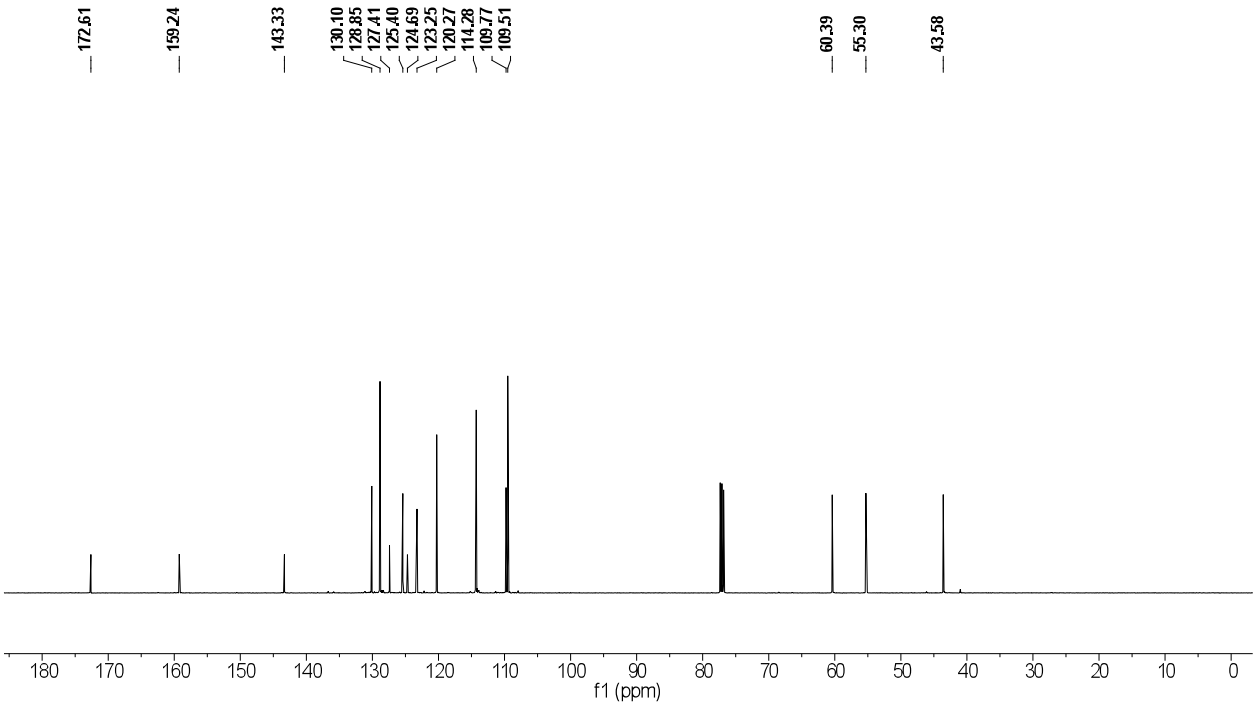
3-(1*H*-pyrrol-1-yl)-1-(4-(trifluoromethyl)benzyl)indolin-2-one (3.4a-1)



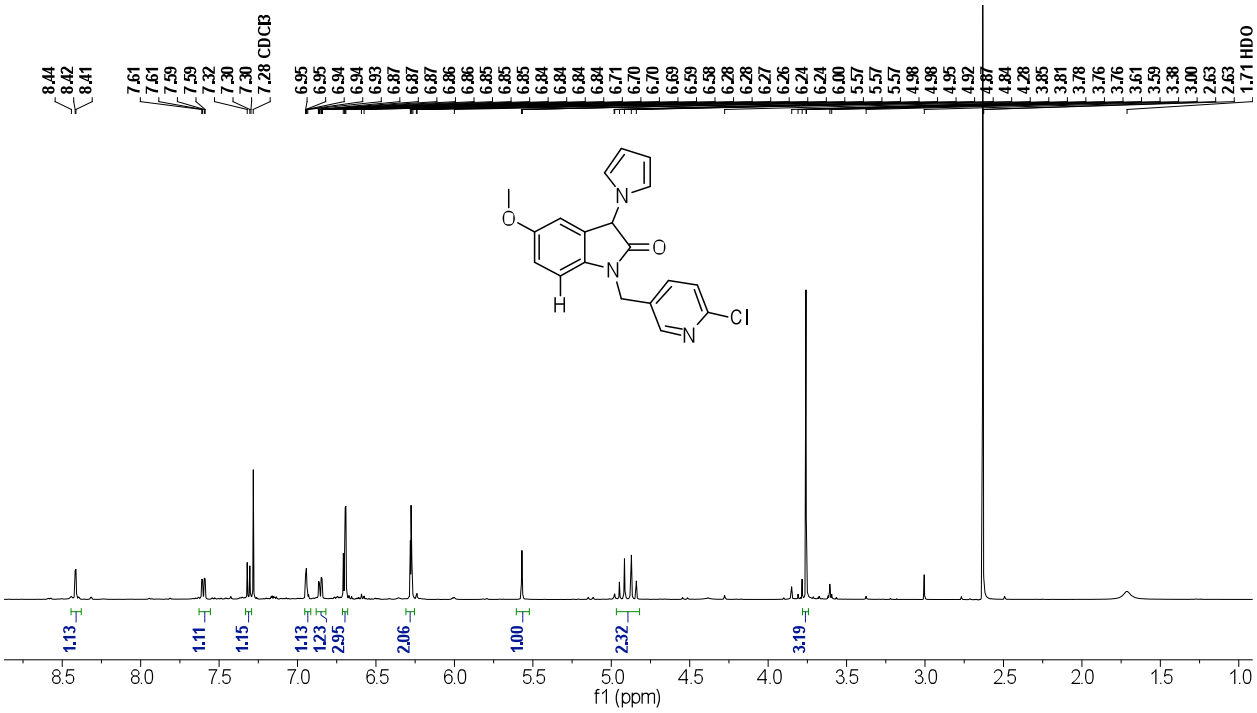


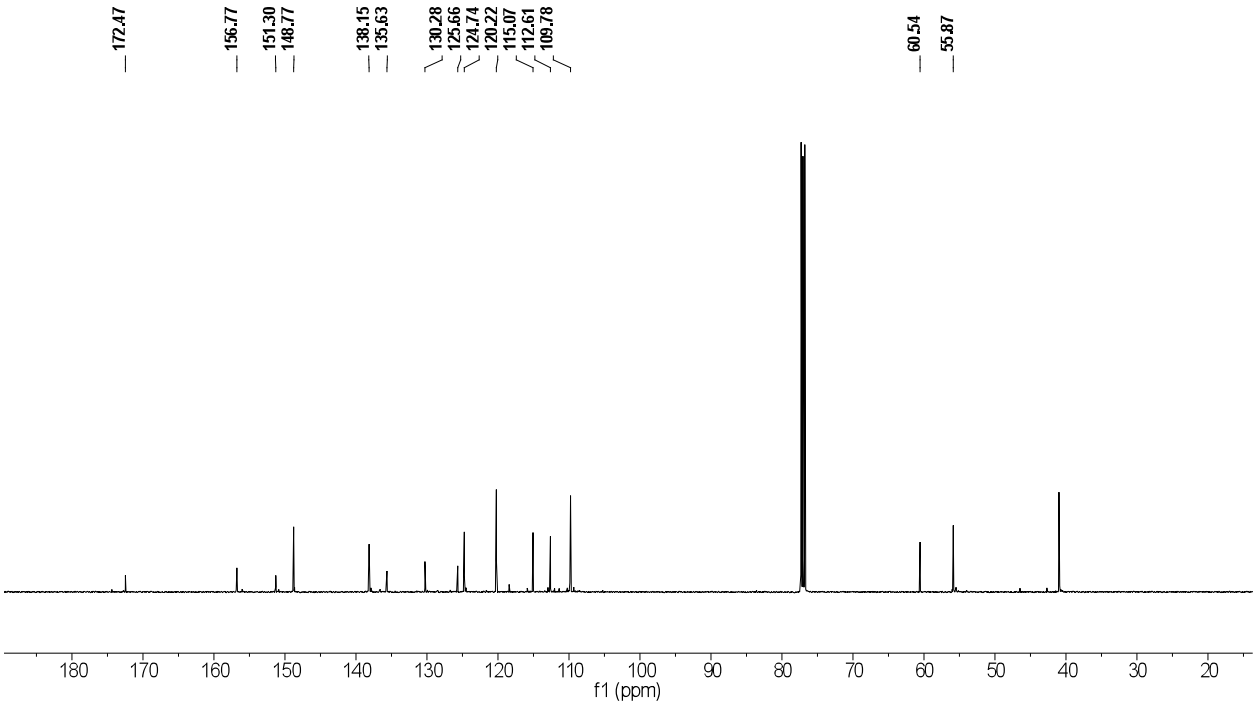
1-(4-methoxybenzyl)-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.4a-1)



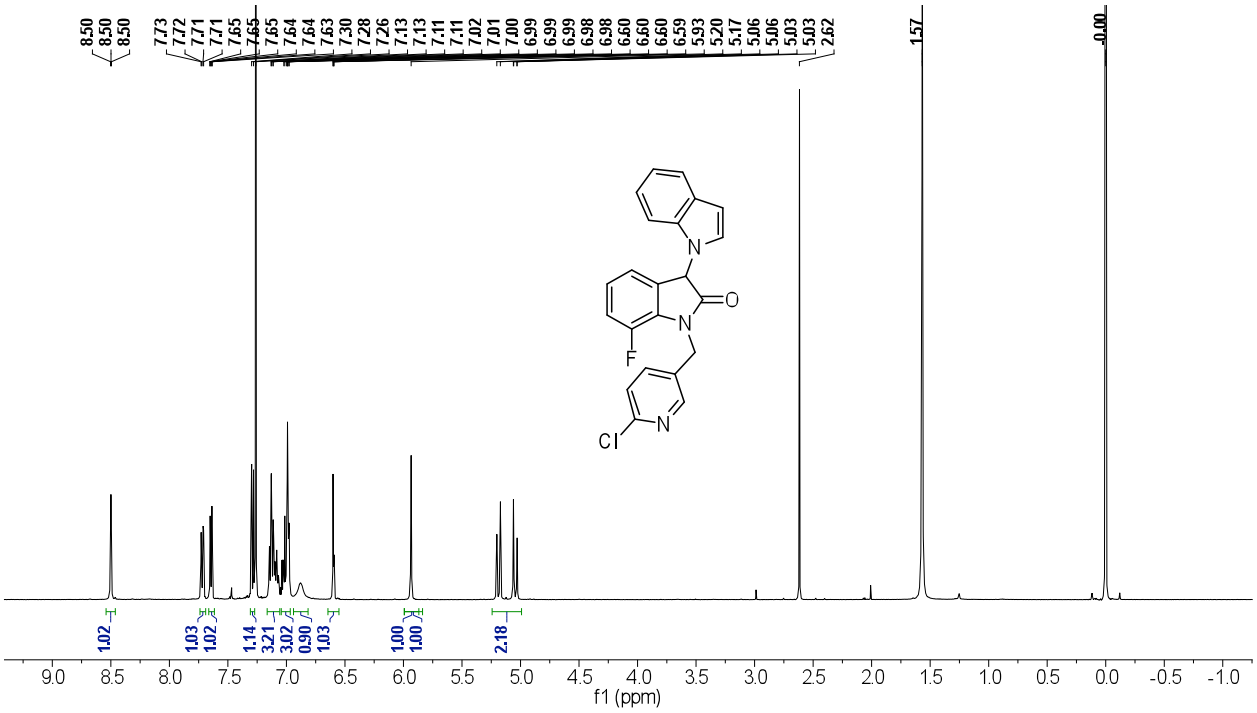


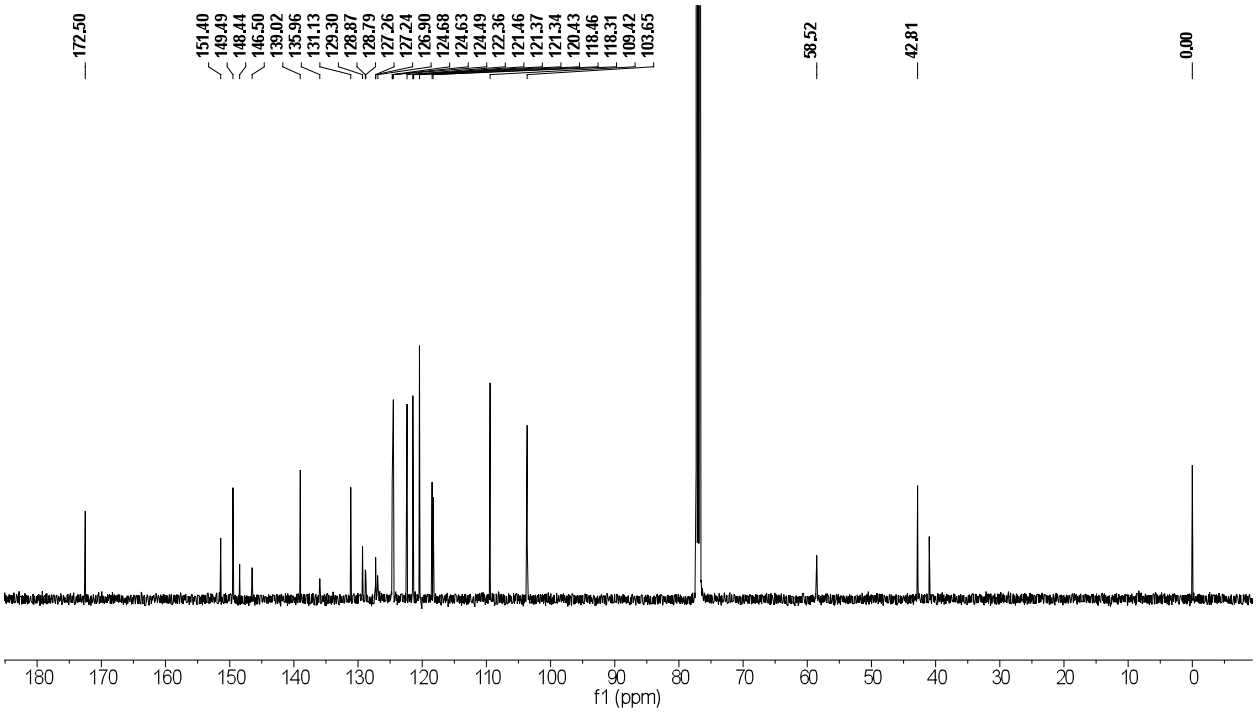
1-((6-chloropyridin-3-yl)methyl)-5-methoxy-3-(1*H*-pyrrol-1-yl)indolin-2-one(3.3b-1)



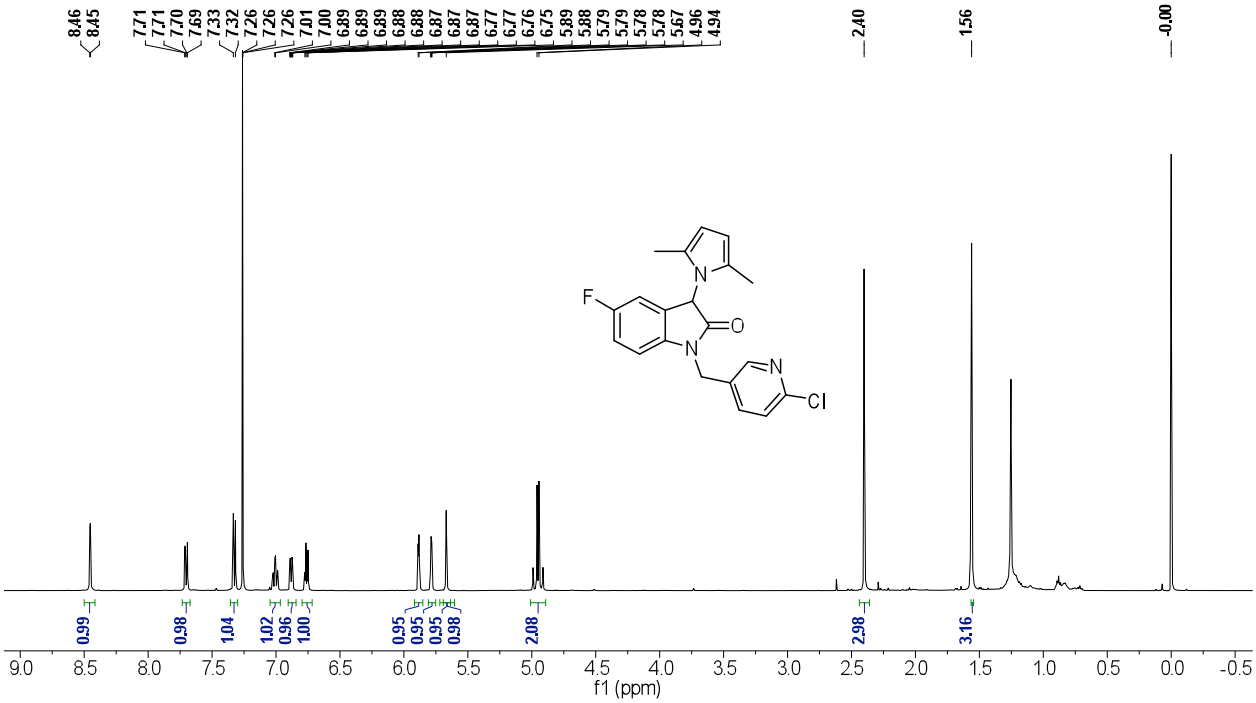


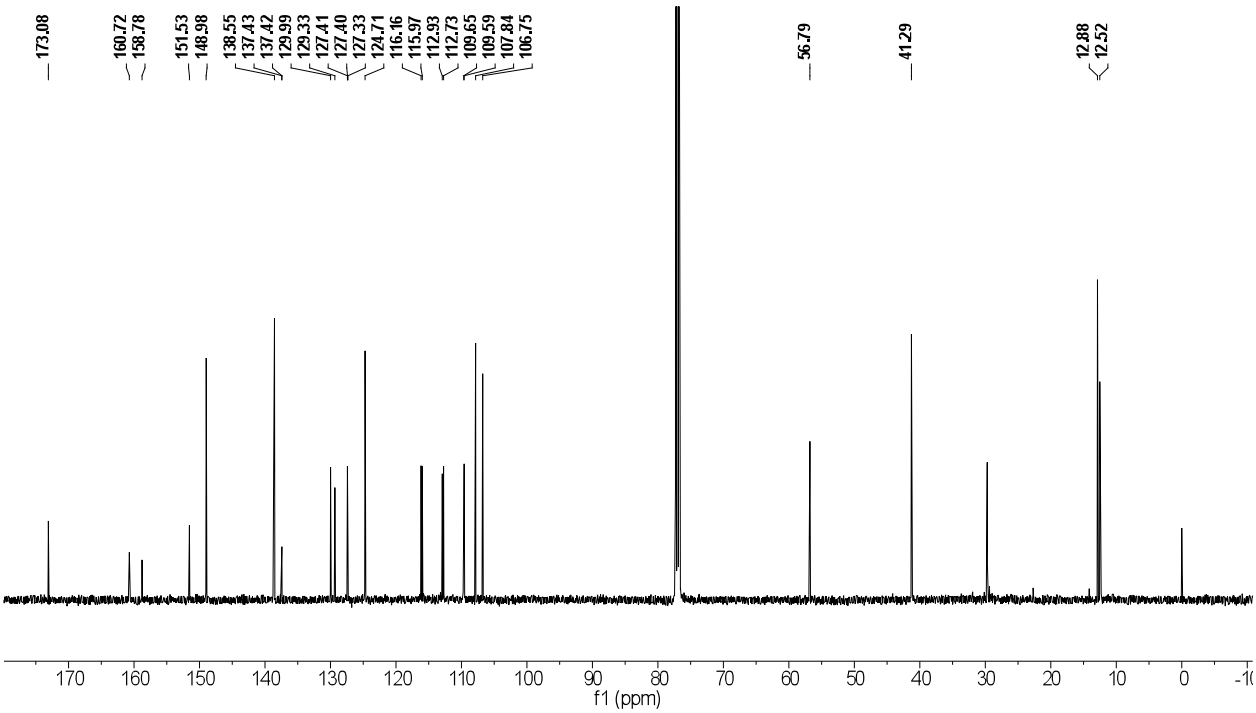
(6-Chloropyridin-3-yl)methyl)-7-fluoro-3-(1*H*-indol-1-yl)indolin-2-one (3.3e-4)



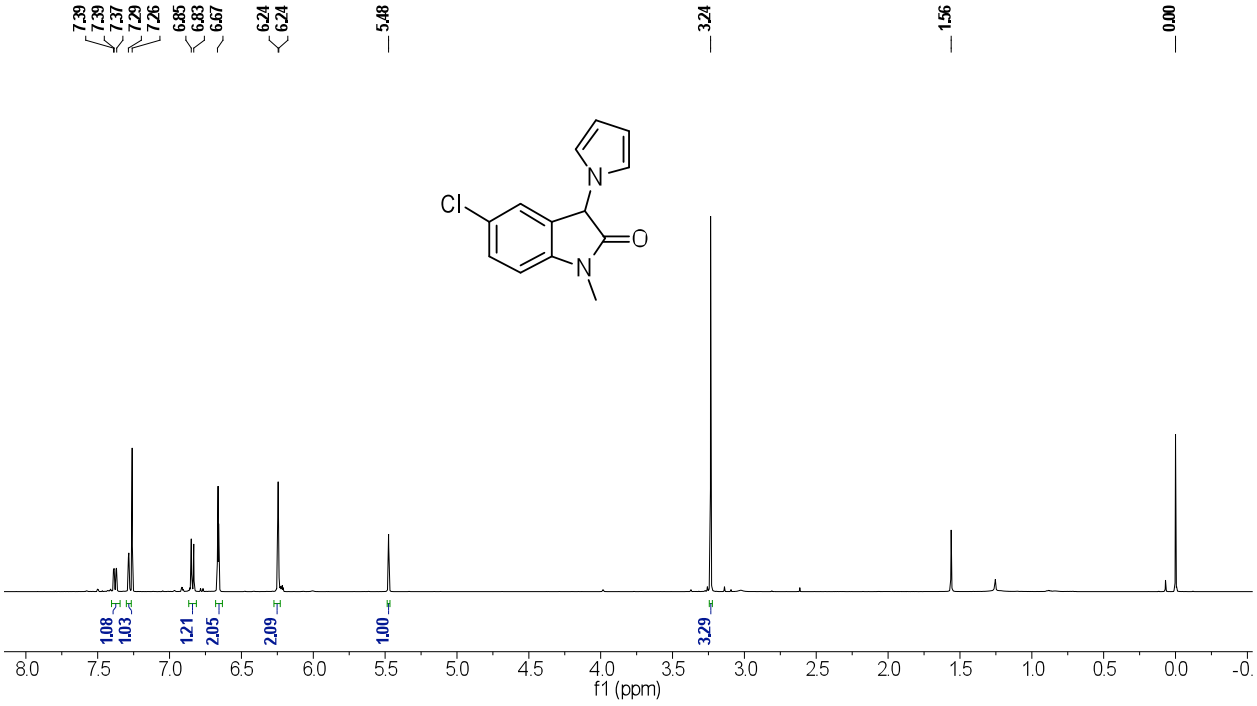


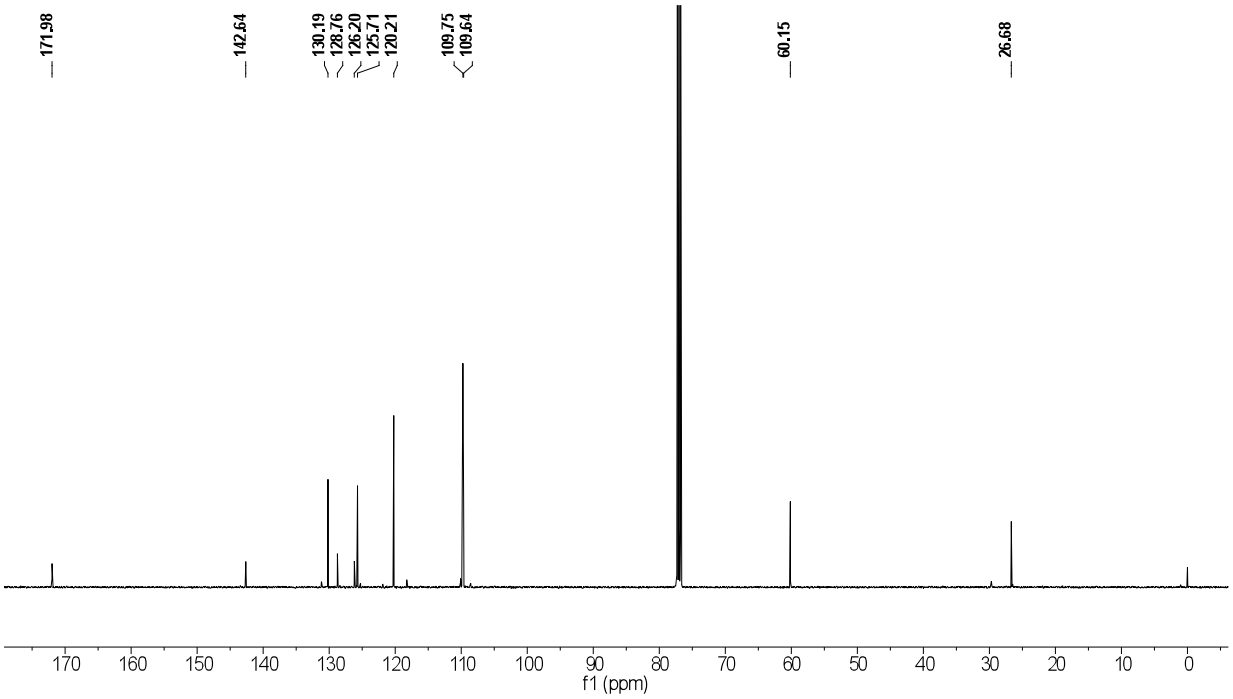
1-((6-chloropyridin-3-yl)methyl)-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoroindolin-2-one (3.3d-2)



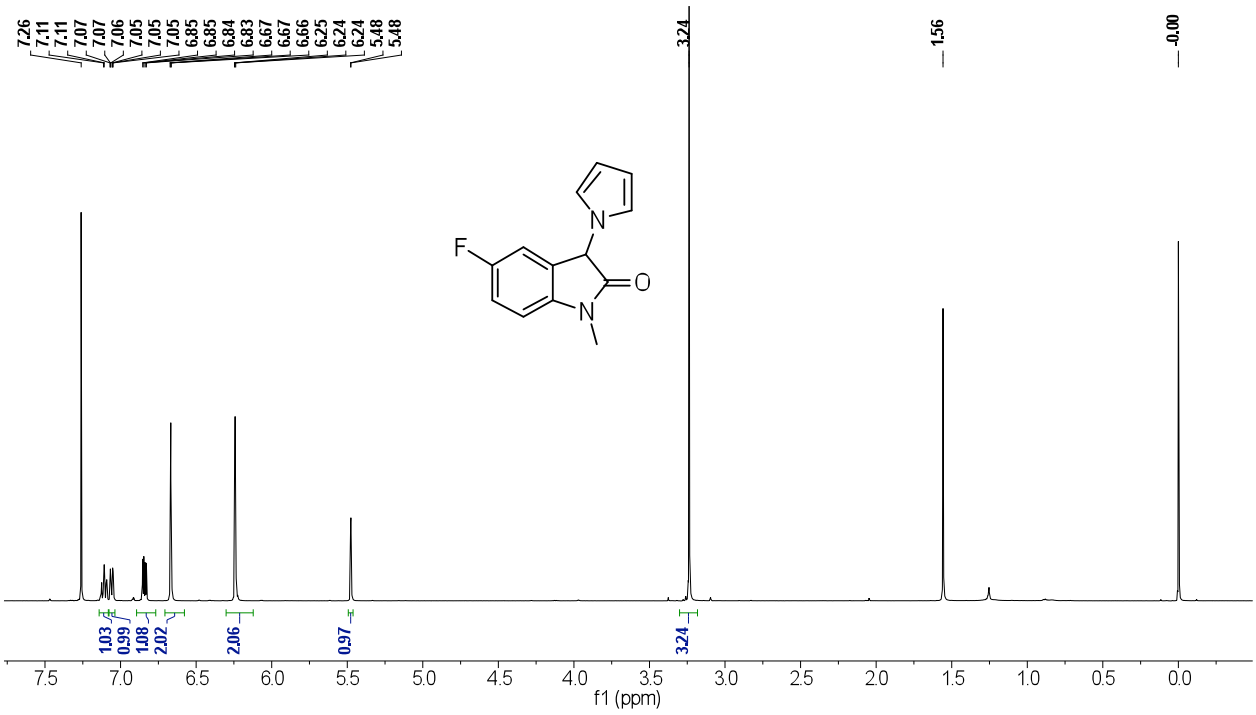


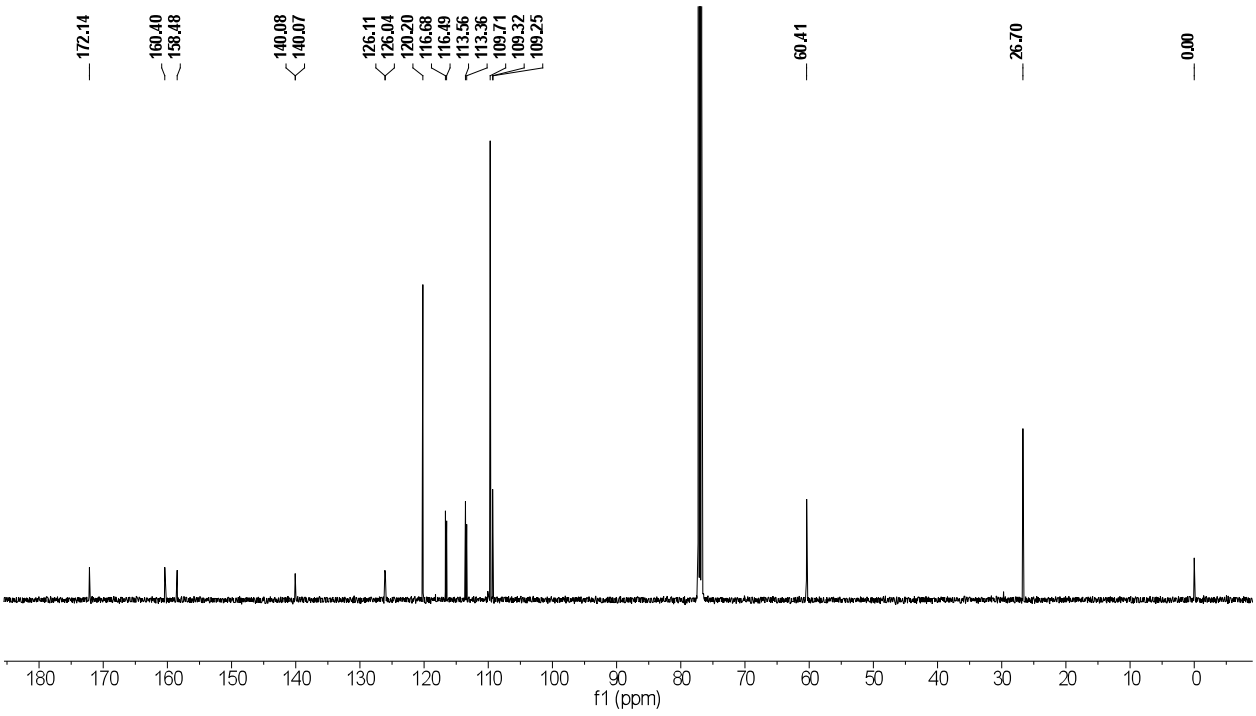
5-chloro-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.5c-1)





5-fluoro-1-methyl-3-(1*H*-pyrrol-1-yl)indolin-2-one (3.5d-1) :

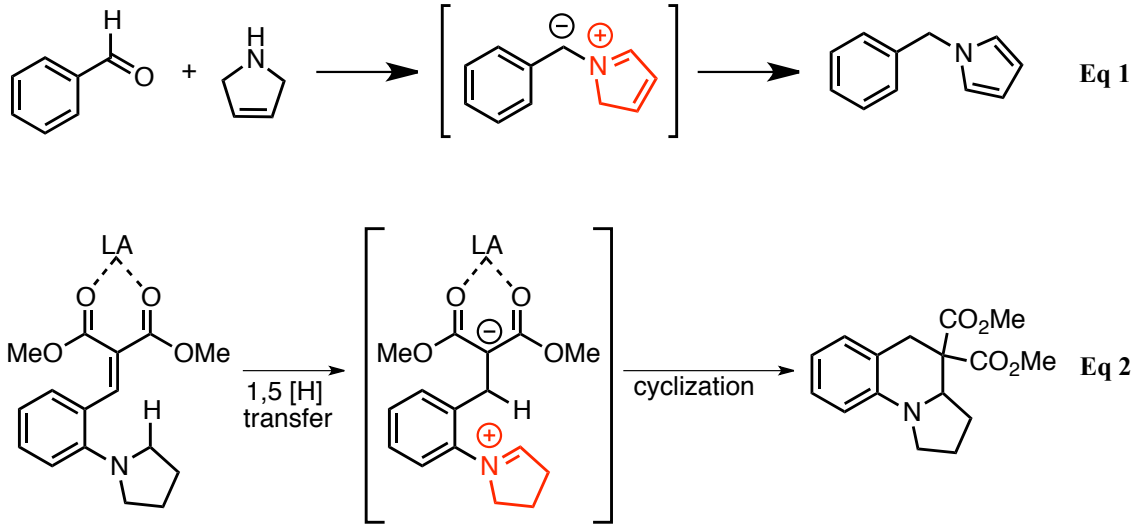




Chapter 4-1 Similarities between the tert-amino effect and redox amination

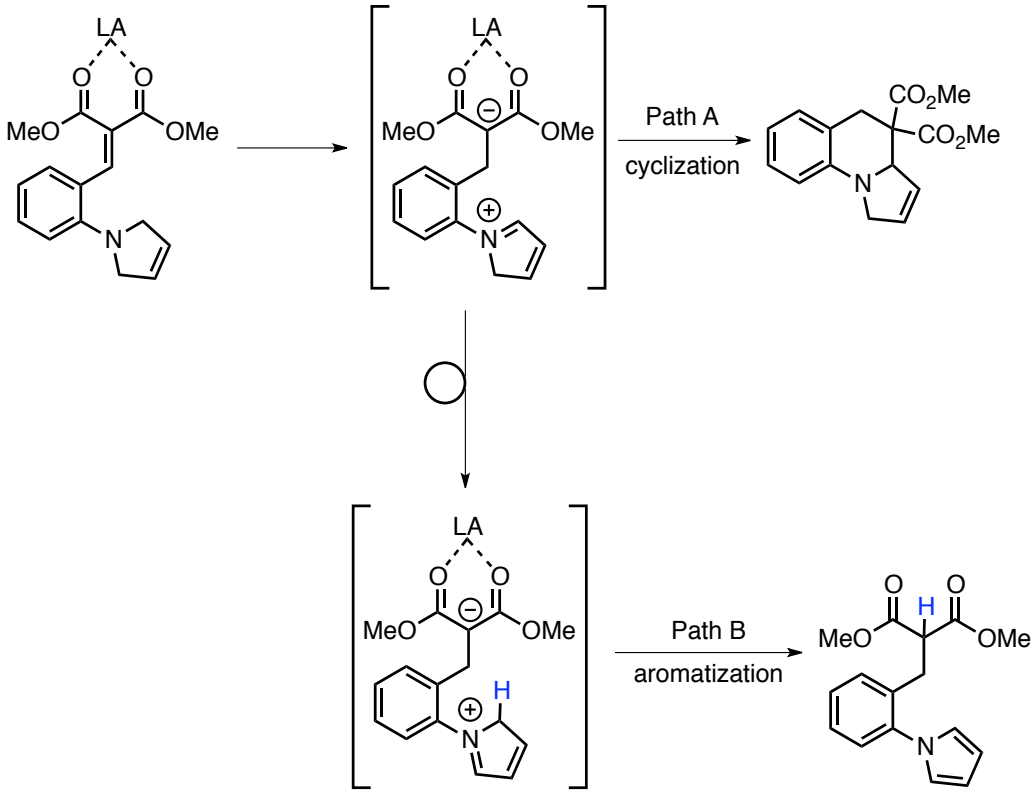
Our group has previously explored the redox amination of pyrrolines.[1] The redox amination of pyrrolines is believed to proceed through an intermediate azomethine ylide that has an internal double bond between the nitrogen and the carbon of the 5-membered ring (Scheme 4-1.1, Eq 1).[2] This is noticeably similar to the intermediate seen in redox isomerizations using the tert-amino effect, particularly those of type 2 (Eq 2).

Scheme 4-1.1: Similarities between Redox Amination and the Tert-Amino Effect



This similarity in mechanism of redox aminations and tert-amino effect reactions lead us to wonder if benzylidene malonate with an ortho pyrroline could be induced to initiate a tert amino effect reaction (Scheme 4-1.2). However, instead of forming the normal carbon-carbon bond (Path A), deprotonation would give a pyrrole and a reduced benzylidene moiety (Path B). Aromatization competing with cyclization had been shown by Reinhoudt with regard to type 1 tert amino effect reactions.[3] Aromatization of pyrrolines to pyrroles was intriguing because it would be a unique extension of redox isomerization, though not redox amination since there would not be a C–N bond formed

Scheme 4-1.2: Pathways for Aromatization vs. Cyclization

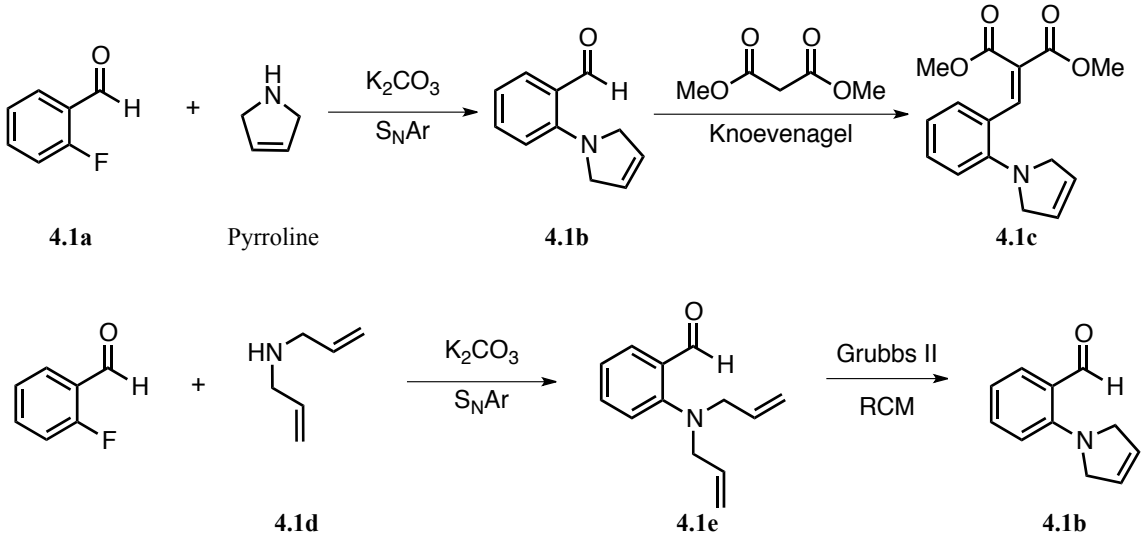


during the reaction. Formation of these two products would also show that redox amination of pyrrolines and the tert amino effect go through similar mechanisms. Additionally, it may be operationally more convenient than previous redox aminations. Pyrrolines, with an unsubstituted nitrogen, are known to undergo oxidation when exposed to air and consequently must be kept under an inert atmosphere. By contrast, pyrrolines with an alkyl group on the nitrogen are more air stable and can be stored with less fear of auto oxidation. These factors led us to investigate whether conditions could be found to favor the formation of pyrroles from intermediates that normally provided cyclization products.

Chapter 4-2 Pyrroles via the Tert-Amino Effect

Before we could investigate the scope of tert-amino effectreaction, we had to synthesize the starting benzylidene malonates. The typical route to such molecules starts from a *o*-fluorbenzaldehyde (**4.1a**, Scheme 4-2.1)[4] and utilizes nucleophilic aromatic substitution to provide an ortho-substituted benzaldehyde **4.1b** followed by a Knoevenagel condensation. While this method was found to work on a small scale, it requires use of excessive amounts of pyrroline. The high cost of pyrroline and the desire to produce large amounts of the starting material lead us to search for an alternative route.

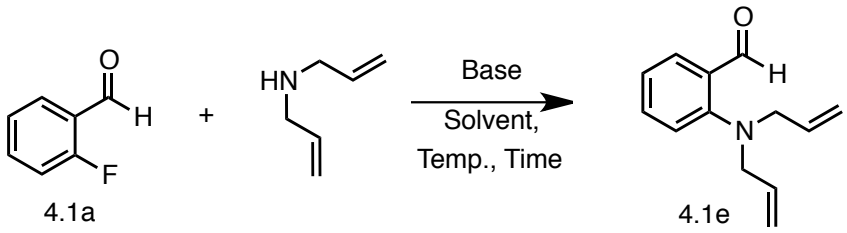
Scheme 4-2.1: Synthesis of 2-Pyrroline Benzylidene Malonates



Diallyl amine (4.1d) is a very inexpensive and air stable amine that is known to undergo ring-closing metathesis (RCM) to give a pyrroline.[5] If diallyl amine would undergo S_NAr with 2-fluorobenzaldehyde to give diallylaminobenzaldehyde (4.1e), the resulting product could then be subjected to RCM and Knoevenagel reactions to give the desired product.

In practice, diallyl amine was found to be a poor nucleophile for S_NAr reactions (Table 4-2.1).

Table 4-2.1: S_NAr Using Diallyl Amine



4.1a 4.1e

Entry	Solvent	Base	Temp(°C)	Time (h)	Ratio 4.1a:4.1e
1	DMF	K_2CO_3	110	12	70:30
2	DMF	K_2CO_3	110	24	48:52
3	DMF	K_2CO_3	110	48	45:55
4	DMF	Cs_2CO_3	110	48	45:55
5	MeCN	K_2CO_3	80	24	80:20
6[a]	DMF	K_2CO_3	140	3	40:60

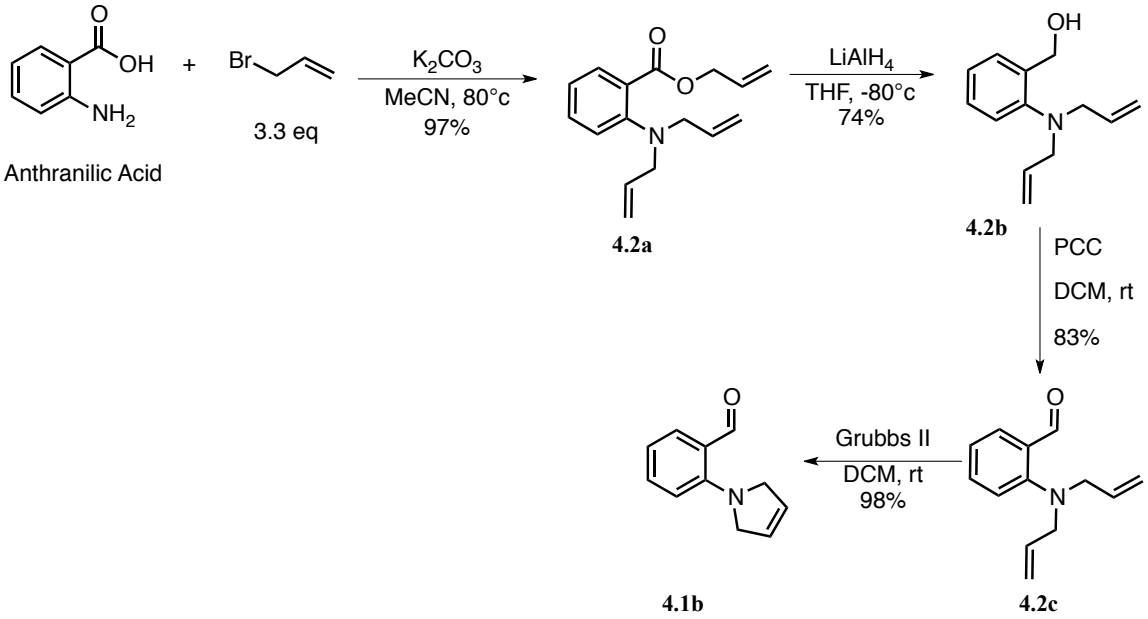
[a] Reaction carried out using microwave

While S_NAr reactions using most heterocyclic amines readily go to completion, the acyclic amine did not go to completion, even when extended reaction times and microwave conditions were utilized. The product and starting material both had similar R_f values and could not be separated by SiO_2 chromatography. While it was found that this mixture of fluoro/diallylamino benzaldehydes could then be subjected to RCM, those products also proved difficult to separate. A route that would allow for simpler isolation of desired products was sought.

It was noticed that anthranilic acid bares the desired nitrogen ortho to a carbonyl and thus could serve as a precursor to our desired amino aldehyde. A synthetic route from

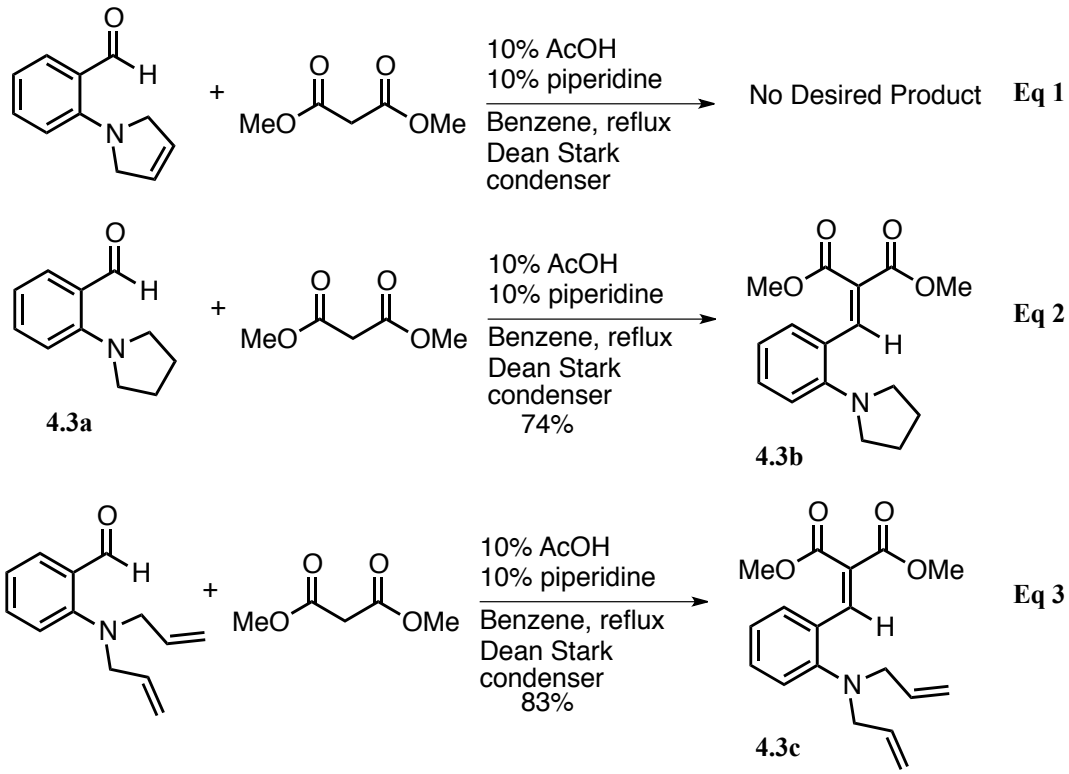
antranilic acid was found that involved triple allylation, ester reduction, oxidation, and finally RCM to afford the desired aldehyde in good yield on a synthesis that easily be scaled to multigrams (Scheme 4-2.2).

Scheme 4-2.2: Optimization of Pyrroline Benzaldehyde



With these results in hand, the Knoevenagel reaction between dimethyl malonate and the 2-pyrrolinobenzaldehyde was undertaken. Initial Knoevenagel conditions were unsuccessful, failing to provide any of the desired product (Table 4-2.2, Eq 1).

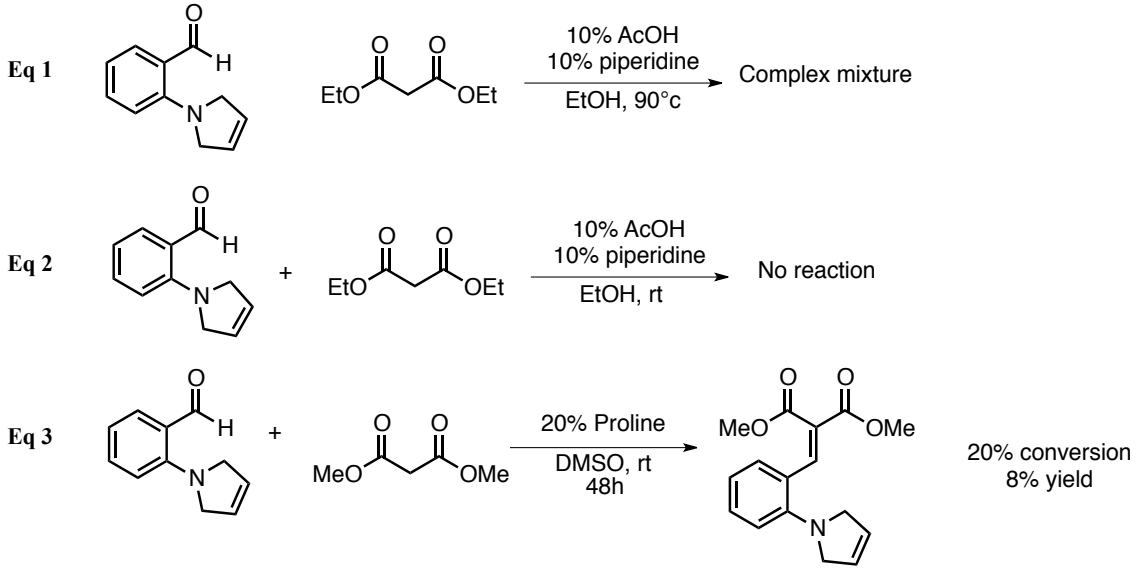
Table 4-2.2: Knoevenagel Reaction Results



To our surprise, thermal Knoevenagel condensation under a number of conditions failed to give the desired product, which was quite puzzling since the similar Knoevenagel of benzaldehyde with pyrrolidines is well known in the literature.[6] One fear was that under these reaction conditions the pyrroline is oxidized to a pyrrole, which is then able to undergo conjugate addition to the benzylidene malonate, either intra or intermolecularly. This appears to be unique to the pyrroline moiety, since the Knoevenagel condensations of diallylamino benzaldehyde and dimethyl malonate proceed without incident (Eq 3). This result led us to screen other solvents that might allow this reaction. It was found that when ethanol was used a solvent, an inseparable

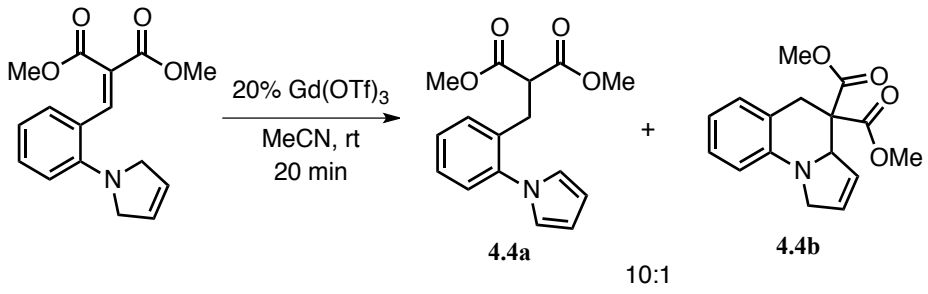
mixture of products was produced (Table 4-2.3, Eq 1). Conducting the same reaction at room temperature produced no reaction (Eq 2). This led us to search for conditions that would allow for the product formation at lower reaction temperatures. It was found that carrying out the reaction at room temperature in DMSO, using proline as a catalyst, did afford the desired condensation product, but in poor yield (Eq 3).

Table 4-2.3: Knoevenagel in Other Solvents



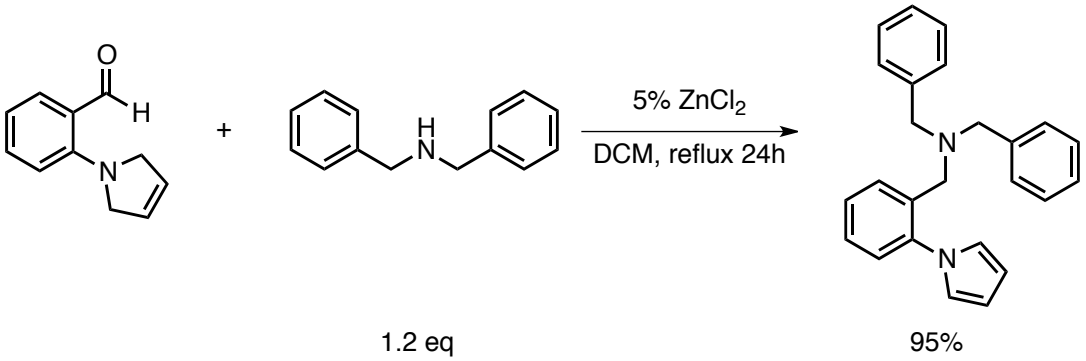
Subjecting pyrroline to reaction with $Gd(OTf)_3$ generated a mixture of aromatization and cyclization in a 10:1 ratio (Scheme 4-2.3). While this was encouraging,

Scheme 4-2.3: Aromatiation vs. Cyclization



the difficulties in synthesizing substrates capable of undergoing this transformation limited this result to a proof-of-concept rather than a viable synthetic method. Such a method for aromatization of pyrrolines was realized fully by Sun and coworkers in early 2015 when they published the pyrrole formation of using 2 pyrroline benzaldehyde and benzyl amines (Scheme 4-2.4).[7]

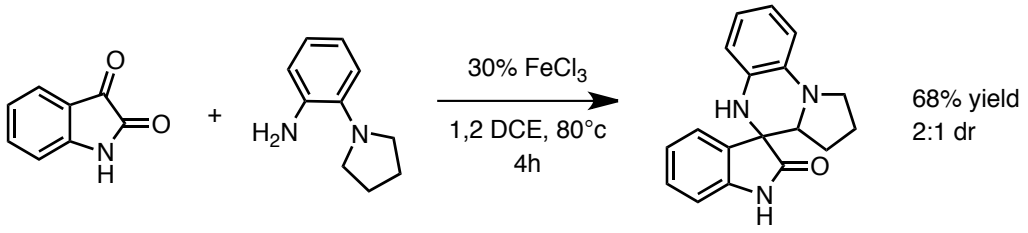
Scheme 4-2.4: Aromatization using Secondary Amines



Chapter 4-3 Pyrrole formation via isatin condensation

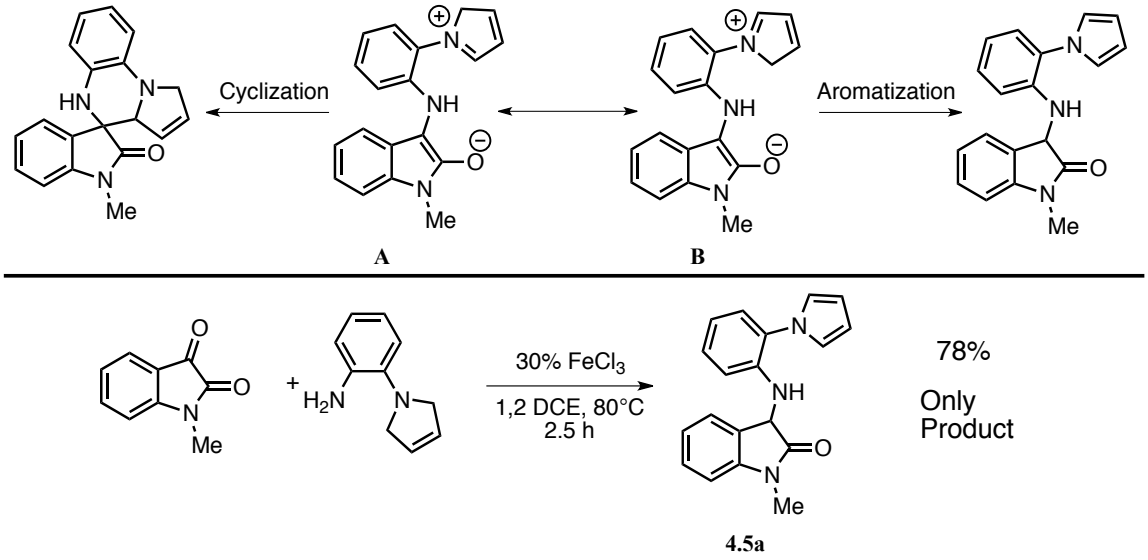
It has been shown by Dr. Kinthada Ramakumar of our lab that anilines bearing a nitrogen-containing heterocycle undergo cyclization with isatins to form spirocycles (Figure 4-3.1).

Figure 4-3.1: Redox Amination of Ortho Anilines and Isatin

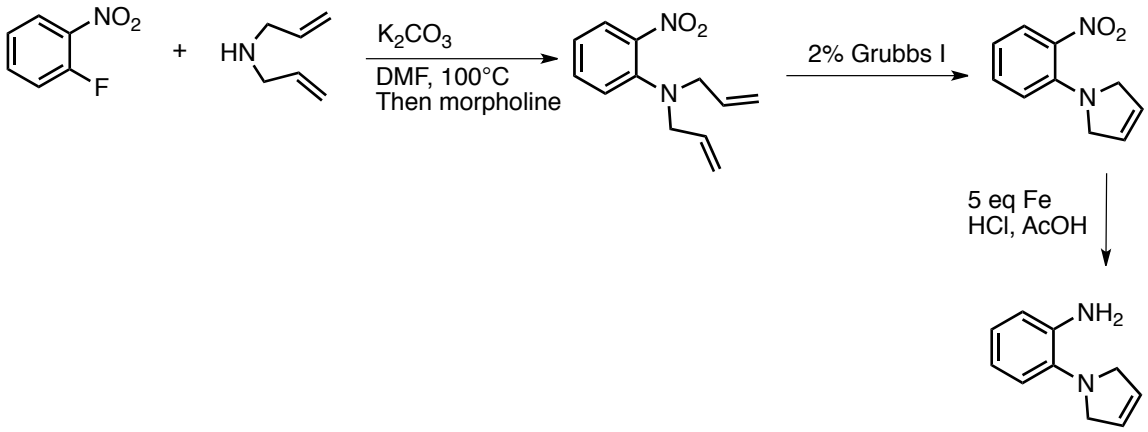


This cyclization is believed to proceed through hydride transfer via a type 2 tert-amino effect, followed by C–C bond formation. This cyclization seems to proceed best when a pyrrolidine is attached to the aniline, since only six member rings with attached aromatic groups (tetrahydroisoquinoline) produced the desired product, and 6- and 7-membered amino anilines were unreactive in this cyclization. This reaction provided a prime opportunity to utilize a 2-pyrrolinoanilie to determine if the reaction could yield a spirocycle via cyclization or a pyrrole via prototropic rearrangement. Both products are possible from the initial hydride transfer (Scheme 4-3.1). The starting aniline was synthesized from 2-nitrofluorobenzene, and diallyl amine.[8] It is of note that, while this reaction does not go to completion at room temperature, the unreacted nitrobenzene can be removed using morpholine, since the S_NAr product of 2-fluoronitrobenzene and morpholine is easily removed via chromatography. RCM and an Fe mediated reduction provide the starting 2-pyrrolinoaniline (Scheme 4-3.2). Gratifyingly, this pyrroline also underwent reaction with isatin, however it by-passed spirocycle formation and produced the pyrrole.

Scheme 4-3.1: Selective Aromatization with Isatin



Scheme 4-3.2: Synthesis of 2-Pyrroline Aniline

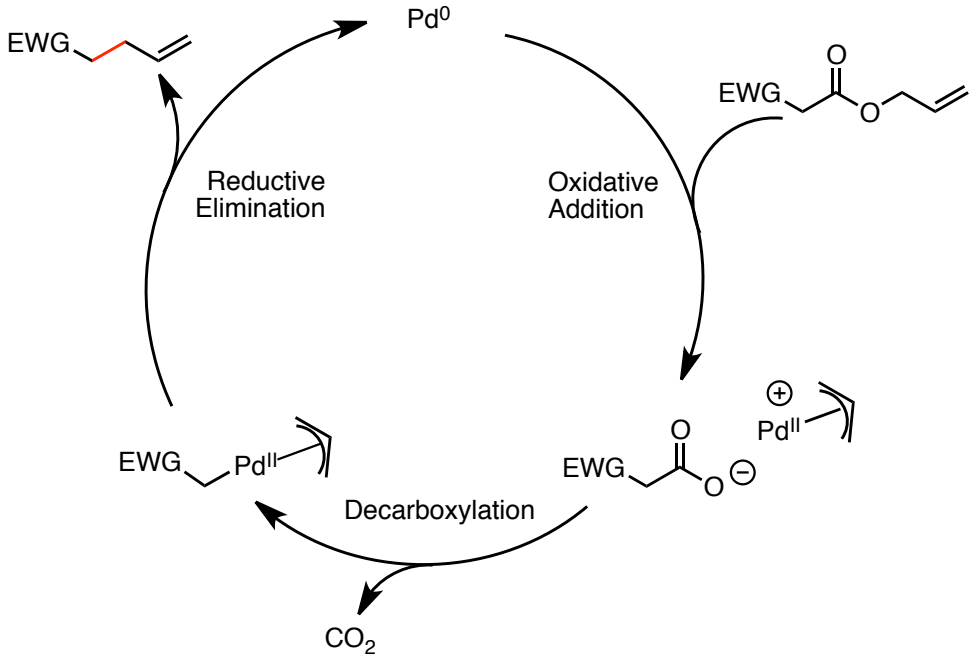


In conclusion, we have shown that the intermediate found in redox amination is similar to that found in reactions in the type 2 tert amino effect. We have also shown that redox amination can be utilized to make pyrroles via a RCM/tert amino effect process.

Chapter 4-4 Allylation of isatin imine

Paramount among all reactions in organic chemistry are those in which a new carbon-carbon bond is formed. These are the key reactions that allow the generation of molecules that are key to modern human life. Any method that can be utilized for this means is worthy of exploration. Palladium-catalyzed decarboxylative allylation (DCA) is one such method.[9] In the most general sense DCA's can be thought of as using palladium to create a new carbon-carbon bond from an allylic ester bearing an electron withdrawing group (Scheme 4-4.1).

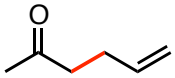
Scheme 4-4.1: Typical Mechanism for Palladium-Catalyzed Decarboxylative Allylation



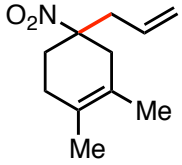
The mechanism typically starts when a Pd^0 oxidatively inserts into an allylic ester, forming a Pd-π-allyl complex. Next, decarboxylation occurs, forming an anion that is stabilized by the electron withdrawing group. Reductive elimination follows, producing an allylated product and regenerating the catalyst, with the only by-product of this reaction being CO_2. Our group has investigated many different electron withdrawing groups in these reactions (Table 4-4.1).[10]

Table 4-4.1: Previously used EWG's

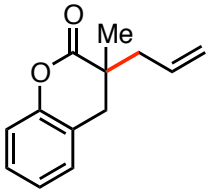
Ketones



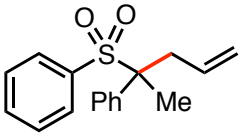
Nitro Alkanes



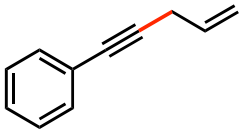
Esters



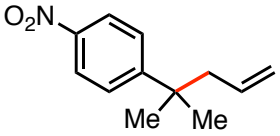
Sulfones



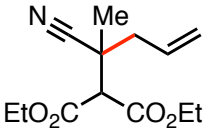
Alkynes



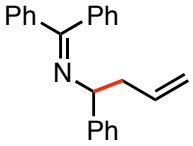
Nitrobenzyl Alkanes



Nitriles

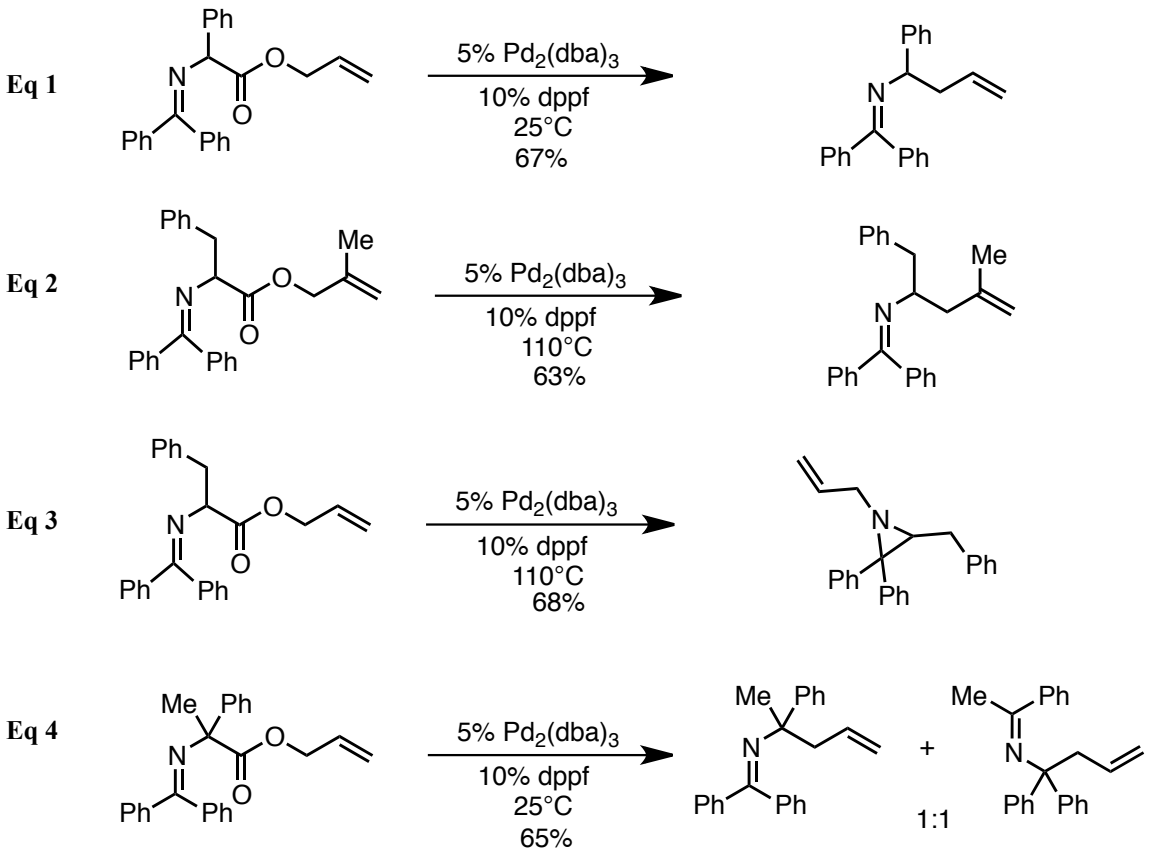


Imines



The functional group that stands out the most of these is the imine, since it is not typically considered a strong electron withdrawing group and they can easily be hydrolyzed. Such imines have been shown to react with the allyl esters of amino acids to give homoallyl amines (Scheme 4-4.2).[11]

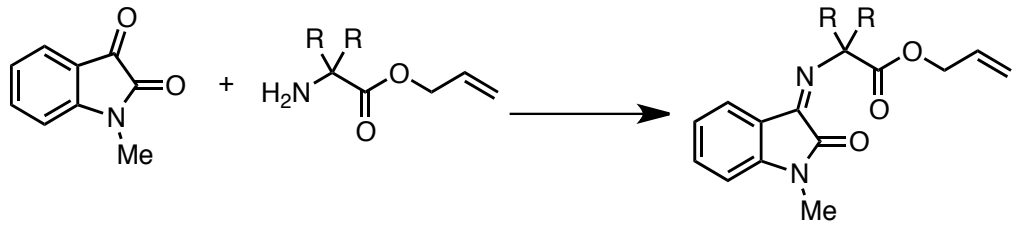
Scheme 4-4.2: DCA's with Benzophenone Imines



When the benzophenone imines were subjected to DCA conditions, several trends were observed (Scheme 4-2.2). Phenyl-substituted amino acids resulted in only the α-allylated imine when allowed to react with palladium at room temperature (Eq 1). Phenylalanine derivatives yielded similar products at elevated temperatures (Eq 2). In contrast to this reactivity with substituted allyl groups, phenylalanine imines bearing an unsubstituted allyl moiety afforded an aziridine product (Eq 3).While mono substituted imino esters only produced one regioisomer, the disubstituted diphenyl imino ester produced a mixture of α and α' allylation products (Eq 4). As part of my ongoing

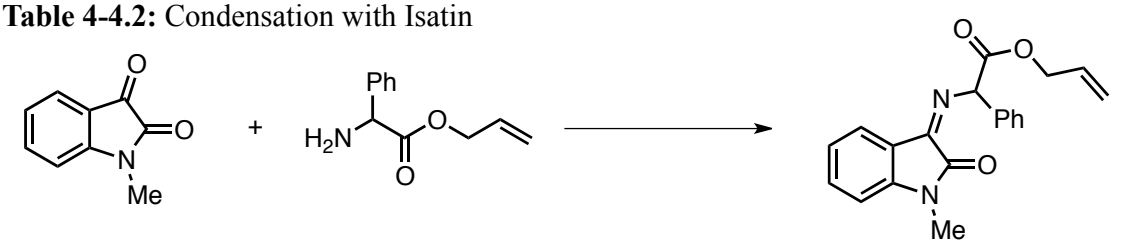
research with isatin derivatives, we wished to study if DCA was applicable to imines other than diphenyl imines, such as isatin derived imines (Scheme 4-4.3).

Scheme 4-4.3: Allyl Amino Acids and Isatins



We initially synthesized the allylic esters of phenylalanine and phenylglycine, those having previously been shown to be reactive as the benzophenone imines. Standard conditions for condensation proved to be ineffective with N-methyl isatin (Table 4-4.2).

Table 4-4.2: Condensation with Isatin

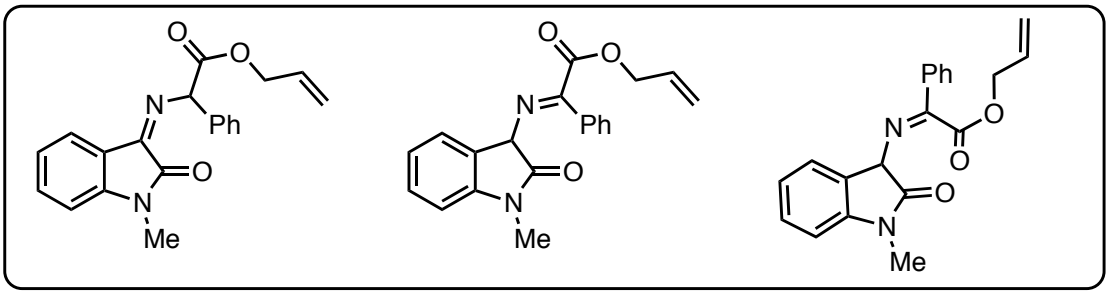


Entry	Solvent	Additive	Temp. (°C)	Time	Yield
1	CH_2Cl_2	$MgSO_4$	RT	12h	0
2	CH_2Cl_2	4A mol sieves	RT	12h	0
3	Allyl-OH	none	80	24h	0
4[a]	Benzene	none	100	12h	68%

[a] Reaction conducted using Dean-Stark conditions

A number of drying agents were used, but it was eventually found that the reaction precedes best in benzene under Dean-Stark conditions (Entry 4). Unfortunately, this resulted in a mixture of isomers of the imine, which we were unable to separate (Figure 4-4.1).

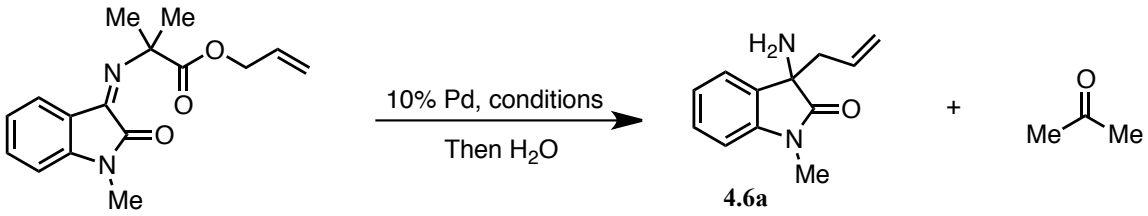
Figure 4-4.1: Isomers of Condesnation



This indicated that the condensation with isatin would require an amino ester that is incapable of isomerization post condensation, such as one containing a quaternary carbon at the α-carbon of the amino ester. It had previously been shown that these amino esters produce a mixture of allylation products with the benzonphenone imines.[11] This prompted us to investigate if the electron-withdrawing amide of isatin would favor allylation exclusively at the 3-carbon of isatin (α' allylation) (Scheme 4-4.4). This would transpose the position of the imine, which could subsequently be hydrolyzed to the primary amine and ketone. For these reasons, we selected to synthesize the allyl amino ester of 2-amino isobutyric acid, which would produce acetone upon hydrolysis.

Synthesis of the isobutyric amino ester follows typical amino acid protection and esterification methods.[12] The deprotection of the boc amino ester by trifluoroacetic acid was found to not readily occur at room temperature, but heating in toluene was found to give the desired product in good yield. The amino ester was then condensed with *N*-methylisatin to form the starting material as a 12:1 ratio of geometric isomers.

Table 4-4.2: Optimization of DCA



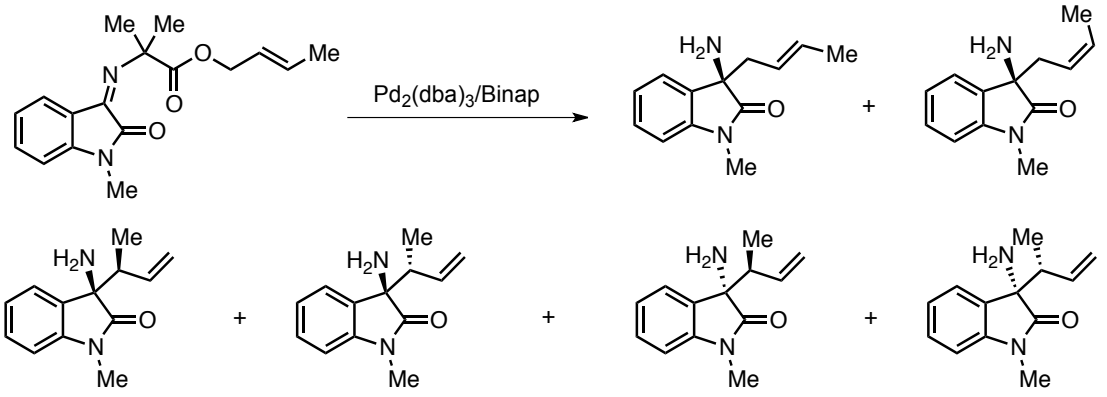
Entry	Pd Source/Ligand	Solvent	Temp (°C)	Time (h)	Conversion (%)	Yield (%)
1	$Pd(PPh_3)_4$	toluene	RT	24	0	NA
2	$Pd(PPh_3)_4$	CH_2Cl_2	RT	24	0	NA
3	$Pd(PPh_3)_4$	THF	RT	24	0	NA
4	$Pd(PPh_3)_4$	toluene	100	1	100	NA[a]
5	$Pd(PPh_3)_4$	THF	60	1	100	NA[a]
6[b]	$Pd(PPh_3)_4$	toluene	100	1	100	NA[a]
7	$Pd_2(dba)_3$/Binap	THF	60	1	100	95
8[b]	$Pd_2(dba)_3$/Binap	THF	60	1	100	94

[a] Product also contained a imputiry of triphenylphosphine. [b] Reaction carried out with 5% Pd catalyst.

Initial studies initiated with the use of $Pd(PPh_3)_4$ as the catalyst. (Table 4-4.2). We did not observe any reaction at room temperature in a number of solvents (Entries 1-3). Upon heating, the reaction was complete within 1 hour (Entry 4). Gratifyingly, the main product observed was the desired 3-allyl oxindole, which upon stirring with water afforded the desired primary amine. While the starting material was completely consumed, the product showed a trace amount of a contaminant with several peaks in the aromatic region of the NMR. To determine whether this was a product of the solvent or catalyst, we switched from toluene to THF (Entry 5), which afforded the desired product

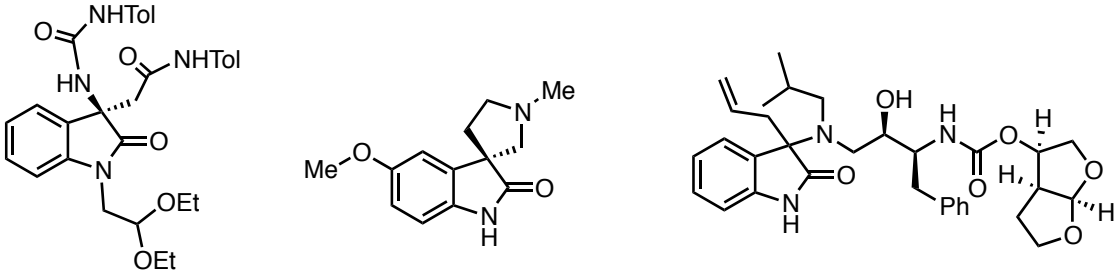
as well, though also with the aromatic impurity. This indicated the impurity was not from some unknown side reaction with toluene. Lowering the amount of catalyst produced full conversion in the same amount of time (Entry 6), and also reduced the amount of contaminant. This led us to believe the unknown was either triphenylphosphine or some byproduct of it. This was confirmed when, after switching to racemic binap ligand, the contaminant was no longer observed and the allylated indolinone was isolated in 95% yield. Importantly, no products corresponding to protonation or regioisomeric allylation were observed. We next chose to examine how diastereoselective and regioselective this reaction can be using the crotyl variant of the aminoisobutyric ester. With $Pd(PPh_3)_4$ there is no selectivity, generating a complex mixture of diastereomers, regioisomers, and cis and trans isomers. Switching the ligand to BINAP did not affect this mixture, making it appear that a more complex system would be needed to select which isomer would be produced (Scheme 4-4.5). The prenyl variant was also made, since it would not produce cis/trans isomers and the large dimethyl moiety would impart much more steric bias on the palladium-π-allyl complex. Unfortunately, this substrate was unreactive under our current conditions.

Scheme 4-4.5: Isomers of Crotyl Esters



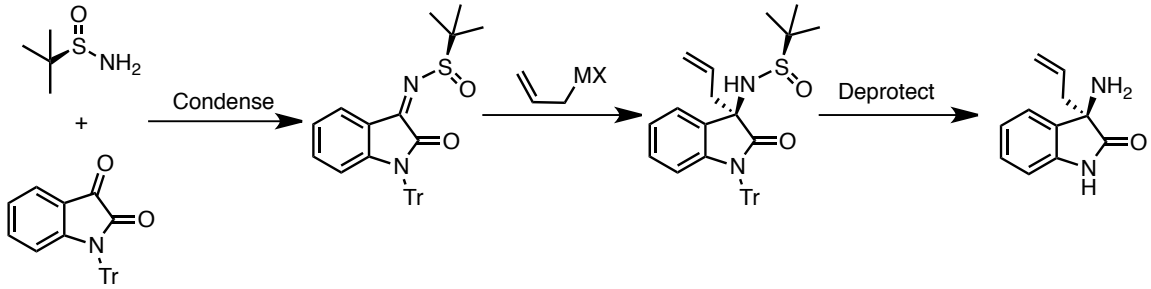
With this data in hand, an enantioselective variant is the most likely next step in future development of this methodology. While many natural products are known which contain a quaternary oxindole,[13] asymetric syntheses of them have areas to improve. To date, the only enantioselective methods to make allylic oxindoles such as (Figure 4-4.2) involves the use of a chiral auxiliary, typically in the form of a chiral sulfoxide (Scheme 4-4.5).[14] While this method is useful, it does require a stoichiometric amount of chiral auxiliary, which must then be cleaved in an additional step. Decarboxylative allylation would be able to circumvent this problem by only requiring a catalytic amount of chiral ligand and leading directly to the desired product.

Figure 4-4.2: Biologically Active 3 Amino Oxindoles



AG-041R Horsfiline HIV Protease inhibitor

Scheme 4-4.6: Typical synthesis of 3,3 disubstitued amino oxindoles



In conclusion, a method for the synthesis of 3-allyl, 3-aminooxindoles via decarboxylative allylation is reported. This method forms a new carbon-carbon bond,

while at the same time forming a new stereogenic center. This reaction produces products under mild conditions, with the only byproducts being CO_2 and acetone. The next step in the formation of this methodology is the development of an enantioselective variant. Before this can be done, an improved synthesis of the starting isatin imine should be developed due to the fact that low yield in this step is detrimental to the overall methodology. On the basis of the chemical literature,[15] these problems can most likely be overcome, thus allowing this decarboxylative allylation to become a powerful method for the synthesis of new carbon-carbon bonds.

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Chapter 4 Supporting Information

General Information

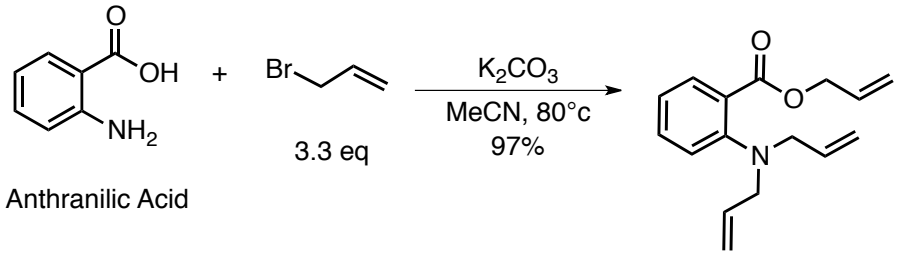
All reactions were run in flame dried glassware under an argon atmosphere. Anhydrous ethanol was used without further purification. Toluene was dried over sodium in the presence of benzophenone indicator. Commercially available reagents were used without additional purification unless otherwise stated. Indoline, indoline 2 carboxylic acid, pyrroline and 2,5 dimethylpyrroline were purchased and used without further purification. Isatins with an unsubstituted N-H as well as 15a, and 17a-17b purchased from commercially available sources and used without further purification. N-substituted isatins were synthesized as described below. TLC analysis was performed with silica gel HL TLC plates w/UV254 from Sorbent Technologies. 60 Å porosity, 230 x 400 mesh standard grade silica gel from Sorbent Technologies was used for flash column chromatography. GC/MS data was obtained using a Shimadzu GCMS-QP2010 SE. ^{1}H and ^{13}C spectra were obtained on a Bruker Advance 500 DRX equipped with a QNP cryoprobe ^{1}H and ^{13}C NMR spectra were referenced to residual protio solvent signals.

Electrospray Ionization spectra were acquired on a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. The instrument was operated at 10,000 resolution (W mode) with dynamic range enhancement that attenuates large intensity signals. The cone voltage was 60eV. Spectra were acquired at 16666 Hz pusher frequency covering the mass range 100 to 1200 u and accumulating data for 2 seconds per cycle. Mass correction for exact mass determinations were made automatically with the lock mass feature in the MassLynx data system. A reference compound in an

auxiliary sprayer is sampled every third cycle by toggling a “shutter” between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles. Samples are presented in acetonitrile (or your solvent here) as a 100ul loop injection using an auto injector (LC PAL, CTC Analytics AG, Zwingen, Switzerland)The Gas Chromatography-Mass Spectrometric data were collected on an Agilent 6890N Gas Chromatograph interfaced with quadrupole mass analyzer (Quattro Micro GC, Waters corp., Milford MA). A 5% phenyl, methyl silicone stationary phase (HP-5MS), 15 meter column with a 0.25" ID was used. The carrier gas was helium and constant flow mode was used to maintain 1.5 mL/min. Injections of 1.0 ul were made into the injector port heated to 240°C and a split ratio of 20:1 was used. The GC thermal gradient was an initial 50°C with a 1 minute hold after which the temperature was increased 25 °C/min to a final temperature of 300° C and held for 2 minutes. Ionization was by electron impact at 70eV and the mass analyzer scanned from 45 to 600 u in 0.5 seconds. The analyzers were tuned to 0.6 u FWHH and data collected in centroid mode.

Synthesis of pyrroline aldehyde

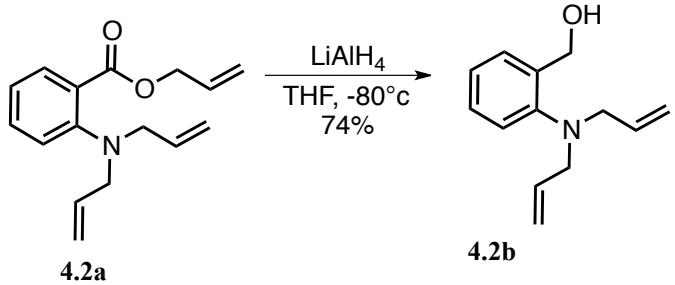
i) 4.2a



4.2a

To a dried, 500 mL round bottom flask was added anthranyllic acid (6.852g) and potassium carbonate (25g). The acetonitrile (250 mL) was added. To this solution was added allyl bromide (24.6mL) dropwise. The reaction was then heated at reflux for 12h. The reaction was then cooled, quenched with saturated ammonium chloride, and placed in a sepratory funnel. The mixture was extracted 3 times with ethyl acetate, brined, dried with magnesium sulfate. The drying agent was filtered off. The solution was then rotovapped down and purified via column chromatography (5% ethyl acetate/hexanes) and yieled 12.47g of **4.2a** as bright yellow liquid (97%)

ii) 4.2b

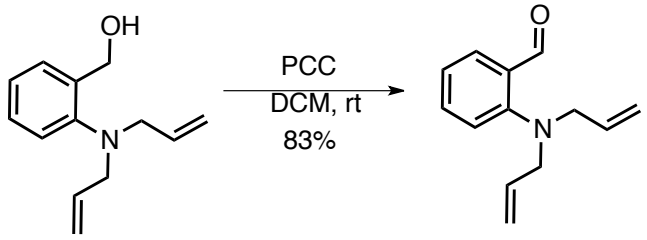


4.2a **4.2b**

To a 2 neck 500 mL round bottom flask was added 1.673g (44 mmol) of $LiAlH_4$. The flask was then sealed and filled with argon, to this was added 200 mL of THF. The reaction was cooled to -80ºC. to this was added, dropwise a solution of 10.285g (40

mmol) of **4.2a** in 50 mL of THF. The reaction was stirred for 2 hours, then was quenched at 0ºC with slow addition of 50 mL of water, followed by 50 mL of 1 M KOH. The reaction was warmed to room temperature transferred to a 1L Erlenmeyer flask. Then 3 g of Rochelles salt was added and the reaction was stirred for 30 minutes. The solution was then transferred to an sepratory funnel. The solution was extracted 3 times with ethyl acetate. The fractions were combined, washed with brine, and dried with magnesium sulfate. The drying agent was filtered off and the product was purified by column chromatography, 30%ethyl acetate/hexanes to give the 6.012g of **4.2b** as a viscous, dull yellow oil.

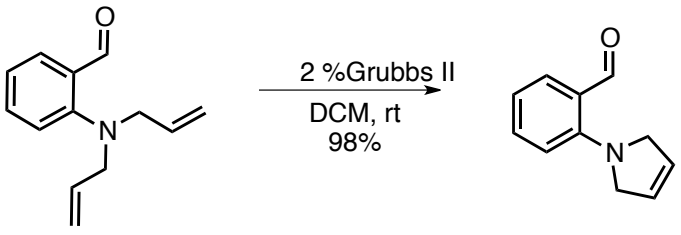
iii) 4.2c



4.2b **4.2c**

In a 100 mL round bottom flask was added 2.03g (10mmol) of **4.2b**. To this was added 1 g of silica gel, and then 50 mL of dichloromethane. Next was added 2.15g of PCC. The reaction was stirred at room temperature overnight. The next day the reaction was filtered, and the reaction flask washed 5 timed and also filtered to remove any residual black goop. The combined fractions were rotovaped down and purified via column chromatography. 3% ethyl acetate/ hexanes) to give1.67g of **4.2c** (83%) as a yellow oil

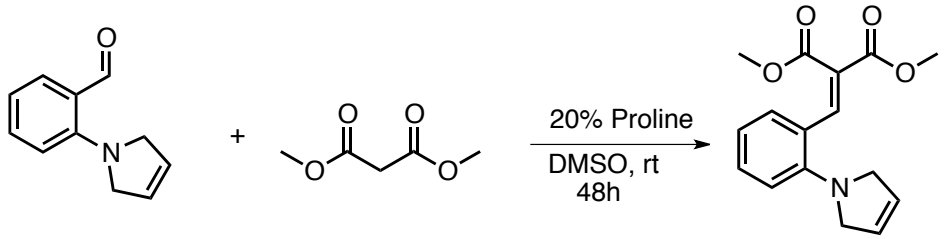
iv) 4.1b



4.2c **4.1b**

To a round bottom flask was added 1.608g (8.3 mmol) of **4.2c**. Next 100 mL of DCM was added, followed by 56mg of Grubbs II. The reaction was stirred at room temperature for 30 minutes, at which time the reaction was filtered through a pad of celite and rotovapped down. The product of this was pure enough to use without further purification. 1.402g of **4.1b** was isolated as a viscous yellow oil (98%)

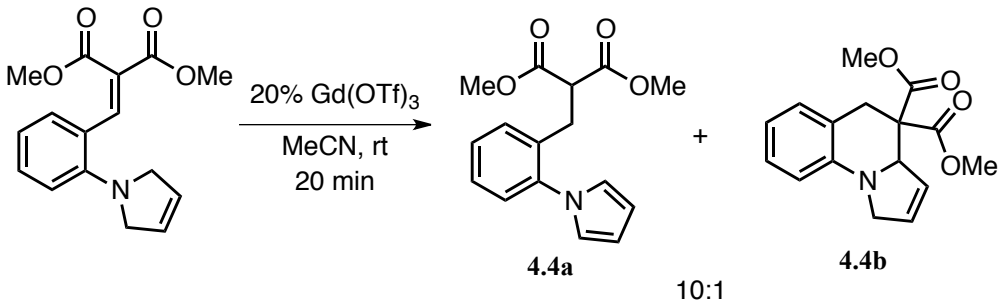
Knovenagle reaction



4.1b **4.1c**

To a round bottom flask was added 20 mL of DMSO, 211 mg of **4.1b** (1.219 mmol) and 139 µl of dimethyl malonate and 28 mg of proline. The reaction was stirred at room temperature for 48 hours at which time TLC analysis indicated two spots, one for starting material and one other . The reaction was stopped, washed through a plug of silica with ethyl acetate, rotovaped down and azeotroped with chloroform several times. NMR of the crude mixture indicated primarily starting material but some of the desired product was present The reaction was purified via column chromatography. The product **4.1c** was made but in low yield (8%) and was recovered as a bright yellow, highly viscous oil.

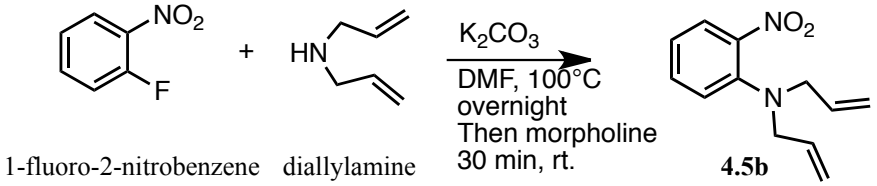
Redox amination of 4.1c



To a stirred solution of 22 mg **4.1c** (0.07mmol) in 7 mL of acetonitrile was added 9.2 mg (20%) of $Gd(OTf)_3$ at room temperature. The reaction turned a bright red color upon addition of the catalyst, which slowly turned into a dull yellow. After 20 minutes the reaction was run through a plug of silica and then he solvent was removed. NMR of the crude product indicated a full conversion of starting material to a mixture of 10:1 **4.4a:4.4b**

Synthesis of 2-amino N-phenyl pyrroline

i) N,N-diallyl-2-nitroaniline

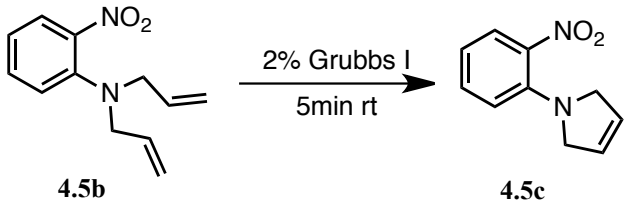


1-fluoro-2-nitrobenzene diallylamine

To a dry 500 mL round bottom flask was added 2.626 g K_2CO_3 (19 mmol), followed by 200 mL of DMF. Then 2 mL of 1fluoro-2-nitrobenzene (18.96 mmol) was added, followed by 2.57 mL of diallyl amine (19 mmol). The reaction was heated to 100ºC and stirred overnight. The next day the reaction was cooled to room temperature and 1mL of morpholine was added to remove any unreacted 2F-Nitrobenzene. The reaction was

stirred for 30 minutes at room temperature. The reaction was then quenched with saturated ammonium chloride, the extracted 3 times with ethyl acetate. The combined extracts were brined, dried with magnesium sulfate, and concentrated via rotory evaporator. The product was purified via column chromatography (1% ethyl acetate/ hexanes) to give the **4.5b** as a bringht yellow liquid in 85% yield

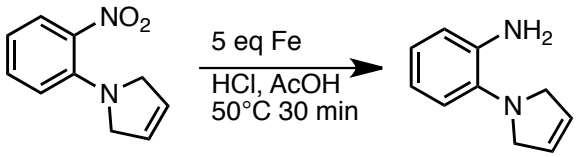
ii) 1-(2-nitrophenyl)-2,5-dihydro-1H-pyrrole



4.5b **4.5c**

To an argon filled schlenk flask with a stir bar was added 3.51g of **4.5b** (16.116 mmoles). This flask was then sealed and wrapped with parafilm and taken into a glove box. To this flask was added 200 mL of dry DCM, and then 264 mg (0.322mmol) of Grubbs I catalyst. The reaction was removed from the glove box. After 5 minutes GC analysis indicated the reaction had gone to completion, so the reaction was filtered through a plug of silica and concentrated to give 3.061g of **4.5c** (99%) as a bright yellow oil.

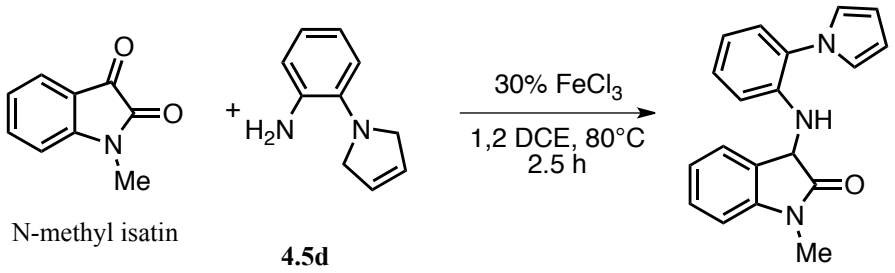
iii) 2-(2,5-dihydro-1H-pyrrol-1-yl)aniline



4.5c **4.5d**

To a 100 mL round bottom flask was added 60 mL of AcOH, followed by 1.208 g of **4.5c** (6.36 mmol), followed by 1.776 g of iron (31.8 mmol). The reaction was heated to 50ºC, at which time several drops of 1M HCl were added until the reaction lost all yellow color. The reaction was stirred for a further 30 minutes, after which time the reaction was diluted with 50 mL of water, the iron salts were filtered off, and the reaction was neutralized with saturated K_2CO_3. The reaction was extracted with 3X60 mL of ethyl acetate, the organic layers were combined, washed with brine, and dried with magnesium sulfate. The product was concentrated and purified via column chromatography (30% ethyl acetate/ hexanes to give 682 mg of **4.5d** (67%) as a dull viscous yellow oil.

Redox amination with isatin



N-methyl isatin **4.5d** **4.5a**

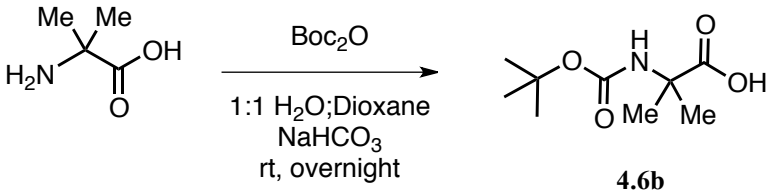
To a 10 mL re-sealable reaction vessel was added 80.05 mg of **4.5d** (0.5 mmol), 80.58 mg of N-methyl isatin (0.5mmol) and 2 mL of 1,2 dichloroethane. To this vessel was then added 24 mg of iron shavings (0.15 mmol) the reaction was heated at 80ºC for 2.5 hours, after which time the reaction was cooled, filtered through a pad of celite, and then

concentrated. The product was then purified by column chromatorgraphy (10-15% ethyl acetate/ hexanes) to give the 118.197 mg of **4.5a** (78%) as a dark orange liquid.

Synthesis of 3 amino oxindoles

Synthesis of allyl amino isobutyric acetate

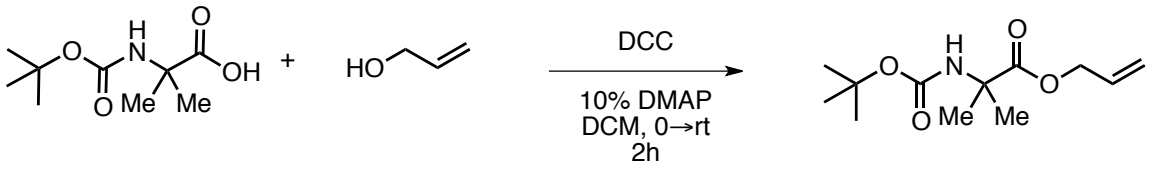
i) N-BOC isobutyric acid



4.6b

To a 250mL round bottom flask was added 2.062g of aminoisobutyric acid (20 mmol). To this was added 40 mL of 1,4 dioxane and 40 mL of water. Next 1.682g of $NaHCO_3$ (20mmol) was added. The mixture was stirred for a few minutes, then slowly 4.365g of Boc_2O was added. The reaction was stirred at room temperature overnight. The next day, the crude mixture was heated on a rotovap to remove the dioxane. The mixture was then acidified with 25 mL of 1M HCl. The mixtue was then placed in a sepratory funnel and extracted 4 times with ethyl acetate. The combined extracts were washed with brine, dried with magnesium sulfate. Removal of solvent gave 3.290 g of **4.6b** (88% yield) as a white powder.

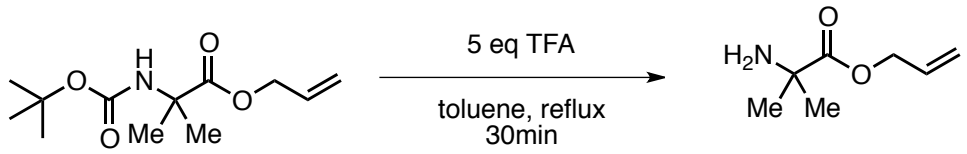
ii) N-Boc isobutyric acetate



4.6c

To a 250 mL round bottom flask was added 2g of **4.6b** (9.846 mmol) followed by 50 mL of dicloromethane. Next was added 680 µl of allyl alcohol (10 mmol). The reaction was cooled to 0ºC and 2.031g of DCC (9.846 mmol) was added, followed by 122 mg of DMAP (1 mmol). The reaction was stirred for 2 hours, after which time the reaction was warmed to room temperature, at which time the reaction was filtered to remove some of the DCU formed. The reaction was then rotovapped down and purified via column chromatography (5% ethyl acetate/ hexanes) to give the 2.106 g of **4.6c** (91%) as a viscous clear solid that upon standing would harden to an opaque white solid.

iii) ally 2 amino isobutyric acetate

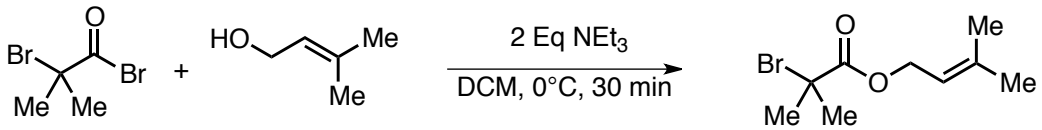


4.6d

To a dried 100 mL round bottom flask was added 2 g of **4.6c** (8.22 mmol), followed by 50 mL of toluene. Next was added 3.14 mL of trifluoro acetic acid(41.1 mmol). The reaction was heated at reflux for 30 minutes, then cooled to room temperature. The reaction was then quenched with 50 mL of saturated $NaHCO_3$. The mixture was then transferred to a sepratory funnel and extracted with 3X 25 mL of ethyl acetate. The combined extracts were brined, then dried with magnesium sulfate. The solvent was removed and the product was purified via column chromatography (30% ethyl acetate/ hexanes to give 1.071 g of **4.6d** (91% yield)as a light yellow liquid the solidified upon standing.

Synthesis of prenyl amino isobutyric acetate

i) prenyl acetate

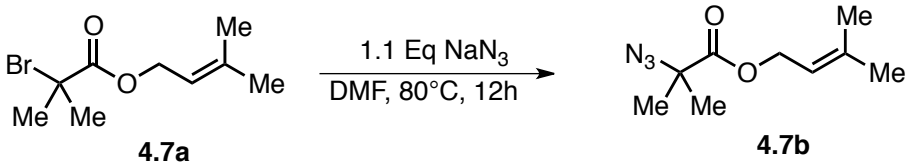


4.7a

To an flame dried 250 mL round bottom flask was added 80 mL of dichloromethane followed by 11.16 mL of triethylamine (80 mmol). Next was added 4.12 mL of Prenyl alcohol (40 mmol). The reaction was cooled to 0ºC in an ice bath and then slowly, 5 mL of alpha bromo isobutyric bromide (40 mmol) was added. The reaction was stirred for 30

minutes, at which point the reaction was placed on a rotory evaporator to remove the DCM. The crude mixture was then suspended in diethyl ether. The ammonium salts were filtered off and the solvent removed to give 9.254 g of **4.7a** as a colorless liquid, which was used without further purification.

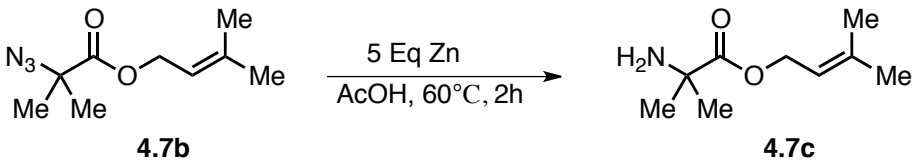
ii) Synthesis of azide



4.7a **4.7b**

To a flame dried 100 mL round bottom flask was added 2.35g of **4.7a** (10 mmol) followed by 50 mL of DMF. Next, 0.721g of sodium azide (11 mmol) was added and the reaction was heated to 80ºC for 12 hours. After this time, the reaction was cooled, quenched with 50 mL of water. The mixture was placed in a sepratory funnel and was extracted with 5x 25mL of ethyl acetate. The organic phases were combined, dried with brine, and dried with magnesium sulfate. The solvent was removed and the product was purified via column chromatography (5% ethyl acetate/hexanes) to give 1.655 g of **4.7b** (84%) as a clear liquid.

iii) Reduction of azide

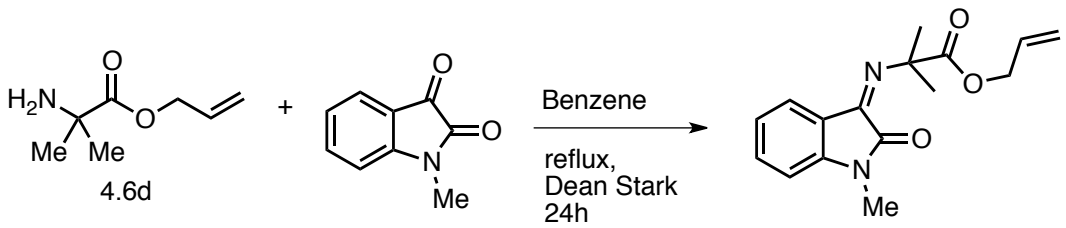


4.7b **4.7c**

To a 100 mL round bottom flask was added 1.1g of **4.7b** (5.58 mmol) and 1.824g zinc (28 mmol) followed by 50 mL of glacial acetic acid. The reaction was heated at 60ºC for

2 hours. The reaction was then cooled to room temperature, diluted with 100 mL of water, and the zinc salts were filtered off. The mixture was then placed in a sepratory funnel, extracted with 3x 50 mL of ethyl acetate, and the organic phases were combined, brined, and dried with magnesium sulfate. The reaction mixture was then purified via column chromatography to give 0.544 mg of **4.7c** (57%) as a viscous fluid that solidified upon sitting.

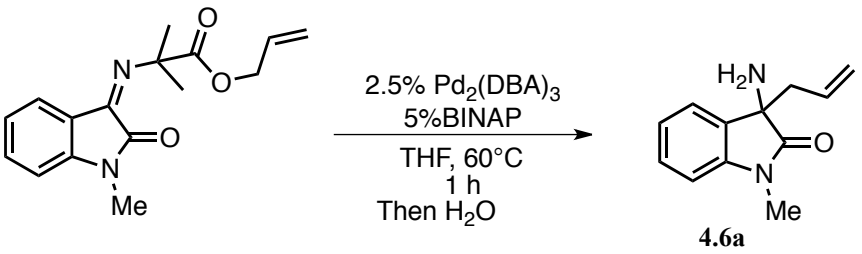
Condensation of aminoester with isatin



4.6f

To a dried, 100 mL round bottom flask was added 1 g of **4.6d** (7 mmol) and 1.124 g of N-methyl isatin, followed by 50 mL of benzene. The flask was then hooked up to a Dean Stark condenser and refluxed for 24 hours. After that time, the reaction was cooled, the solvent was removed and the product was purified via column chromatography, 50%ethyl acetate/hexanes). Care was taken to ensure the product did not come into contact with water. After removal of solvent, 879 mg of **4.6f** (44% yield) was isolated as a bright yellow solid.

Synthesis of 3,3 bisoxindole

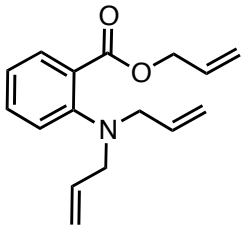


4.6a

To a dried, 10 mL schlenk flask in a glove box was added 11.4 mg of $Pd_2(DBA)_3$ (0.0125 mmol) and 15.5 mg of racemic BINAP (0.025 mmol), followed by 2 mL of dry THF. The flask was sealed and removed from the glove box. The catalyst and ligand were allowed to stir at room temperature for 5 minutes. At which point 143mg of **4.6f** (0.5mmol) in 3 mL of THF was added via syringe. The reaction was heated at 60ºC for 1 hour. At that time the reaction was cooled to room temperature and 1 mL of water was added and the reaction was stirred for 5 minutes. Next the reaction was placed in a sepratory funnel, and extracted with 3X 5 mL of ethyl aceate. The combined layers were washed with brine, dried with magnesium sulfate, and purified via column chromatography (2% methanol/ dicloromethane) to give 95.1 mg of **4.6a** (94% yield) as a yellow oil.

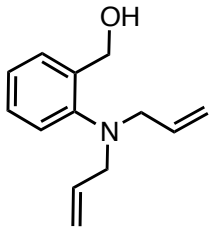
Spectral data for new compounds

4.2a): allyl 2-(diallylamino)benzoate.



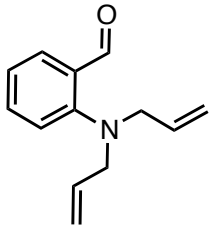
^{1}H NMR (400 MHz, $CDCl_3$) 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.3, 1.7 Hz, 1H), 7.05 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.94 (td, *J* = 7.7, 1.0 Hz, 1H), 6.06 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.86 (ddt, *J* = 16.2, 10.2, 6.0 Hz, 2H), 5.44 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (ddd, *J* = 10.4, 2.6, 1.2 Hz, 1H), 5.13 (m, 4H), 4.82 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.78 (d, *J* = 6.0 Hz, 4H).

4.2b): (2-(diallylamino)phenyl)methanol



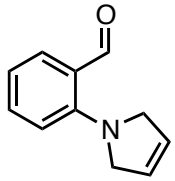
^{1}H NMR (400 MHz, $CDCl_3$) 7.08 (m, 4H), 5.83 (ddt, *J* = 16.7, 10.2, 6.5 Hz, 2H), 5.28 (s, 1H), 5.13 (m, 4H), 4.82 (s, 2H), 3.61 (d, *J* = 6.5 Hz, 4H).

4.2c): 2-(diallylamino)benzaldehyde



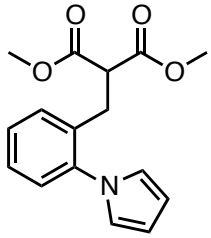
^{1}H NMR (400 MHz, CD_2Cl_2) 10.38 (d, *J* = 0.6 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.3, 7.2, 1.8 Hz, 1H), 7.16 (m, 1H), 7.08 (m, 1H), 5.94 ? 5.83 (m, 2H), 5.24 (dddd, *J* = 13.2, 10.2, 3.0, 1.4 Hz, 4H), 3.83 (dt, *J* = 5.9, 1.3 Hz, 4H).

4.1b): 2-(2,5-dihydro-1H-pyrrol-1-yl)benzaldehyde



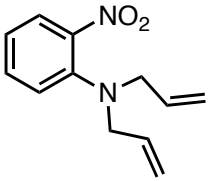
^{1}H NMR (400 MHz, $CDCl_3$)10.14 (s, 1H), 7.73 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.42 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H), 6.82 (dd, *J* = 17.4, 8.0 Hz, 2H), 5.94 (s, 2H), 4.22 (s, 4H).

4.4a); dimethyl 2-(2-(1H-pyrrol-1-yl)benzyl)malonate



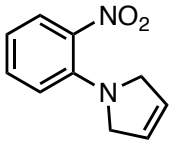
^{1}H NMR (400 MHz, $CDCl_3$) 7.32 (d, *J* = 2.0 Hz, 4H), 6.81 (t, *J* = 2.1 Hz, 2H), 6.36 (t, *J* = 2.1 Hz, 2H), 3.64 (s, 6H), 3.24 (d, *J* = 3.2 Hz, 3H).

4.5b): *N*,*N*-diallyl-2-nitroaniline



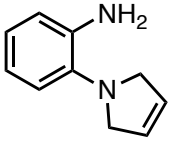
^{1}H NMR (400 MHz, $CDCl_3$) 7.65 (m, 1H), 7.33 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.88 (m, 1H), 5.71 (m, 2H), 5.14 (m, 4H), 3.75 (dd, *J* = 6.0, 1.3 Hz, 4H).

4.5c): 1-(2-nitrophenyl)-2,5-dihydro-1H-pyrrole



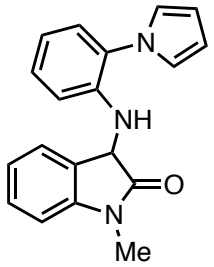
^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (m, 1H), 7.50 (m, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 5.92 (s, 2H), 4.10 (s, 4H).

4.5d): 2-(2,5-dihydro-1H-pyrrol-1-yl)aniline



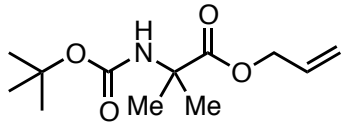
1H NMR (400 MHz, CDCl3) 7.26 (d, *J* = 7.9 Hz, 1H), 7.00 (m, 1H), 6.84 (m, 2H), 6.06 (d, *J* = 4.3 Hz, 2H), 4.53 (s, 2H), 4.18 (s, 4H).

4.5a); 3-((2-(1*H*-pyrrol-1-yl)phenyl)amino)-1-methylindolin-2-one



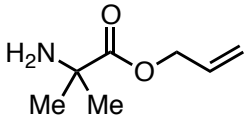
NMR (500 MHz, $CDCl_3$) 7.25 (dd, *J* = 11.2, 4.3 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.06 (m, 2H), 6.96 (td, *J* = 7.6, 0.7 Hz, 1H), 6.77 (dd, *J* = 5.2, 3.1 Hz, 3H), 6.72 (dd, *J* = 10.9, 4.5 Hz, 2H), 6.24 (t, *J* = 2.1 Hz, 2H), 4.86 (d, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 7.4 Hz, 1H), 3.13 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** 175.20, 143.66, 142.39, 129.50, 129.03, 128.04, 127.44, 126.61, 124.21, 123.08, 122.02, 118.33, 112.60, 109.66, 108.52, 56.53, 26.44.**HRMS** Predicted ($C_{19}H_{17}N_3O$) 303.1372 Actual 303.1362

4.6c): allyl 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoate



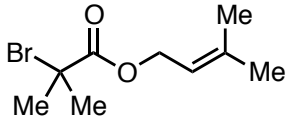
1H NMR (400 MHz, CDCl3) 5.92 (ddt, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.34 (ddd, *J* = 17.2, 3.0, 1.5 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.05 (d, *J* = 1.1 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.02 (s, 1H), 1.52 (s, 6H), 1.44 (s, 9H).

4.6d): allyl 2-amino-isobutyrate



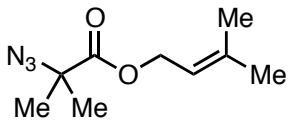
1H NMR (400 MHz, CDCl3) 5.70 (dddd, *J* = 10.5, 5.6, 2.7, 1.4 Hz, 1H), 4.97 (m, 2H), 4.30 (m, 2H), 1.56 (s, 2H), 1.14 (dd, *J* = 5.3, 3.4 Hz, 6H).

4.7a): 3-methylbut-2-en-1-yl 2-bromo-2-methylpropanoate^{1}H



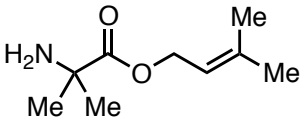
^{1}H NMR (400 MHz, $CDCl_3$) 5.22 (m, 1H), 4.59 (d, *J* = 7.1 Hz, 2H), 1.86 (s, 6H), 1.70 (s, 3H), 1.66 (s, 3H).

4.7b): 3-methylbut-2-en-1-yl 2-azido-2-methylpropanoate



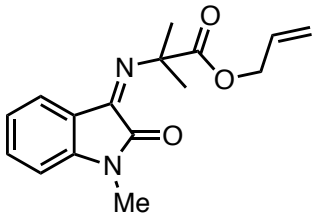
^{1}H NMR (400 MHz, $CDCl_3$) 5.38 (tdd, *J* = 5.8, 2.8, 1.4 Hz, 1H), 4.67 (dd, *J* = 15.5, 7.3 Hz, 2H), 1.79 (s, 3H), 1.75 (s, 3H), 1.50 (d, *J* = 3.9 Hz, 6H).

4.7c): 3-methylbut-2-en-1-yl 2-amino-2-methylpropanoate



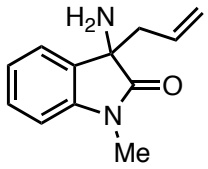
^{1}H NMR (400 MHz, $CDCl_3$) 6.49 (s, 2H), 5.26 (dd, *J* = 14.0, 6.9 Hz, 1H), 4.60 (d, *J* = 7.2 Hz, 2H), 1.68 (s, 3H), 1.64 (s, 3H), 1.58 (s, 6H).

4.6e):allyl 2-methyl-2-((1-methyl-2-oxoindolin-3-ylidene)amino)propanoate



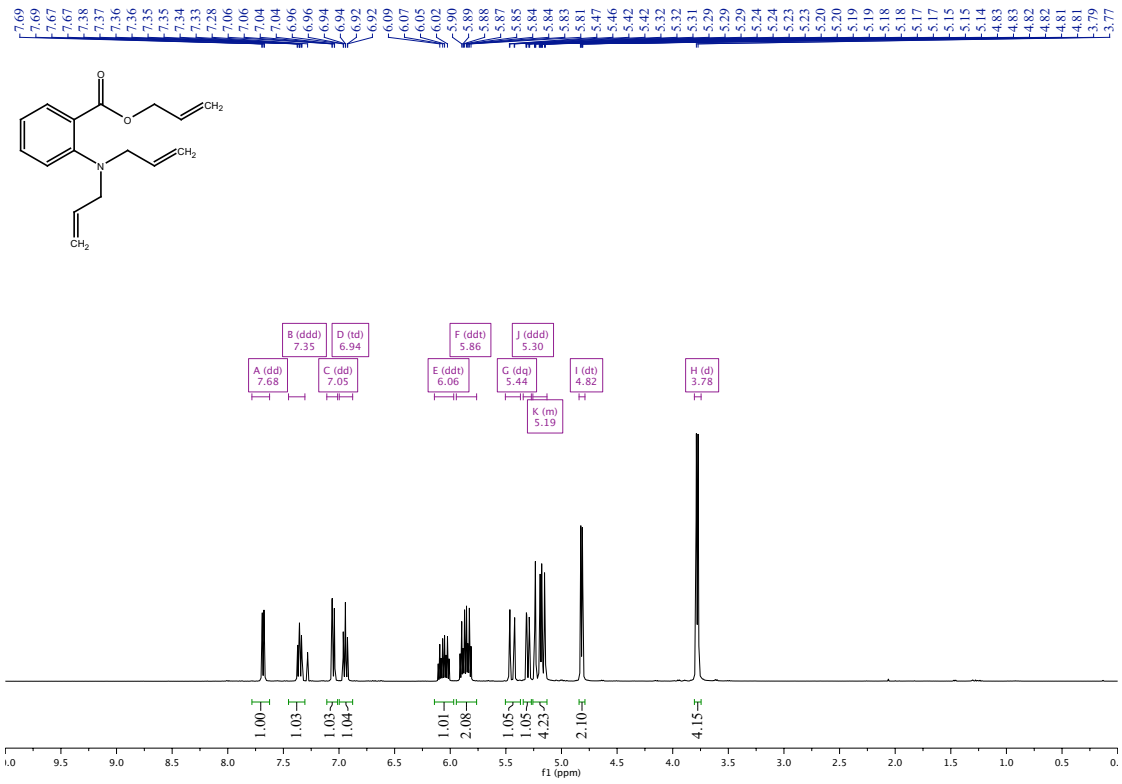
1H NMR (400 MHz, CDCl3) 7.50 (d, *J* = 7.4 Hz, 1H), 7.19 (m, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.69 (m, 1H), 5.10 (m, 1H), 5.03 (t, *J* = 13.3 Hz, 1H), 4.47 (d, *J* = 5.7 Hz, 2H), 3.01 (s, 3H), 1.62 (s, 6H**). ^{13}C NMR (101 MHz, $CDCl_3$)** 173.27, 157.39, 153.33, 145.99, 138.34, 132.98, 132.42, 124.82, 123.59, 122.93, 122.23, 121.63, 117.68, 110.04, 108.46, 65.06, 63.97, 27.63, 27.10, 26.03, 25.72. **(HRMS)** Calculated ($C_{16}H_{18}N_2O_3$) 283.1617 Found 283.1620

2.6a): 3-allyl-3-amino-1-methylindolin-2-one 1H NMR

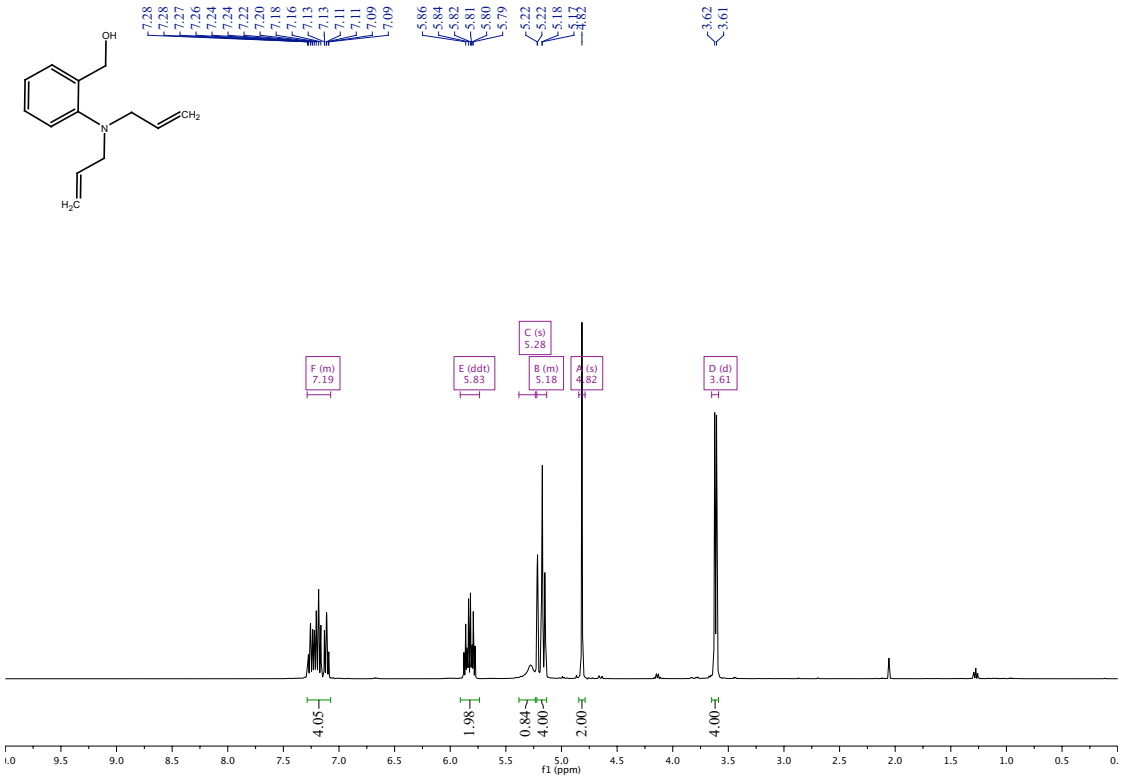


1H NMR (500 MHz, CDCl3) 7.27 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H), 7.21 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.47 (dddd, *J* = 16.9, 10.1, 8.1, 6.6 Hz, 1H), 4.87 (m, 2H), 3.09 (s, 3H), 2.33 (m, 2H), 1.66 (s, 2H). **13C NMR (126 MHz, CDCl3)** 178.96, 142.09, 130.42, 130.33, 127.91, 122.74, 121.70, 118.54, 107.08, 76.43, 76.38, 76.18, 75.92, 59.84, 42.40, 25.09. (**HRMS)**Calculated ($C_{12}H_{14}N_2O$+H) 203.2603 Found 203.2608

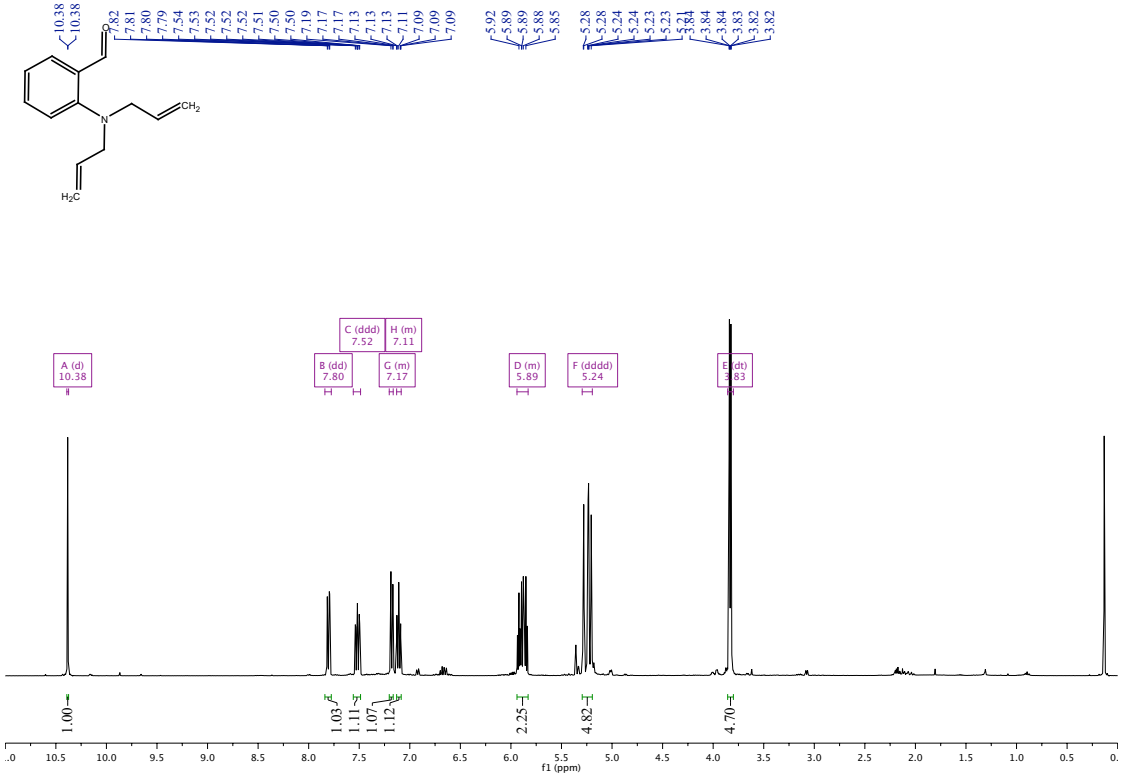
Spectra for new compounds
4.2a



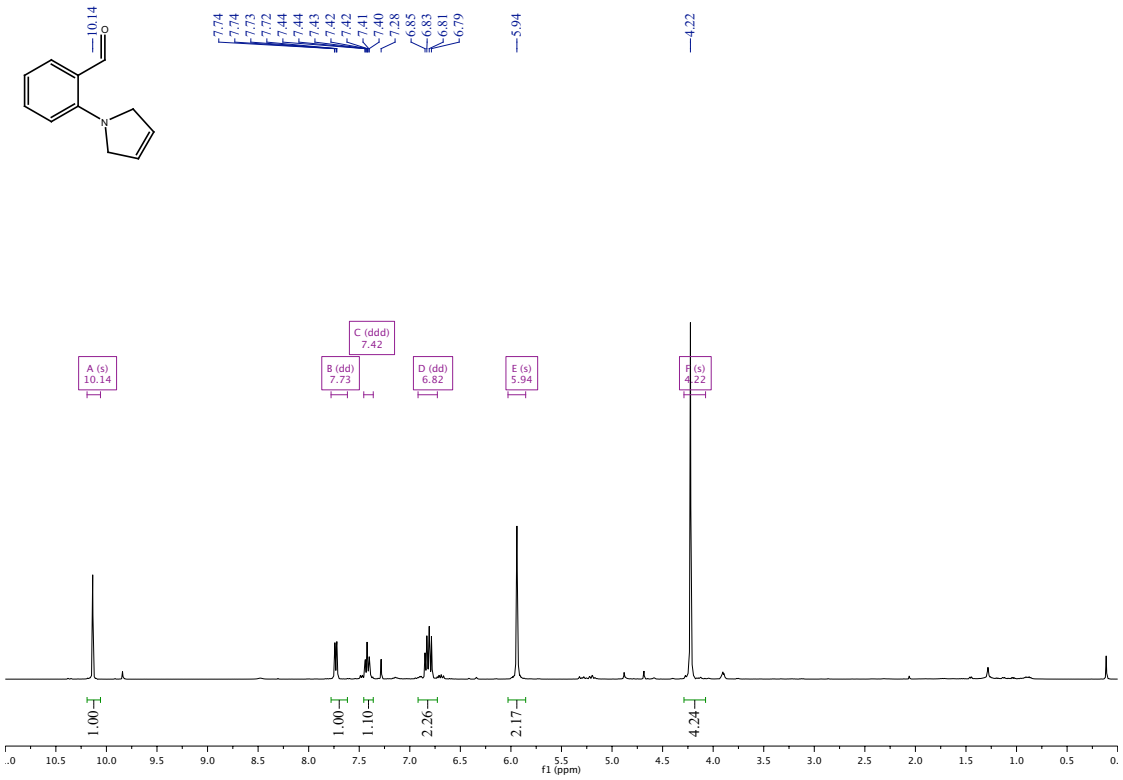
4.2b


OH
N
CH2
H2C
F (m) 7.19
E (ddt) 5.83
C (s) 5.28
B (m) 5.18
A (s) 4.82
D (d) 3.61
4.05
1.98
0.84
4.00
2.00
4.00
f1 (ppm)

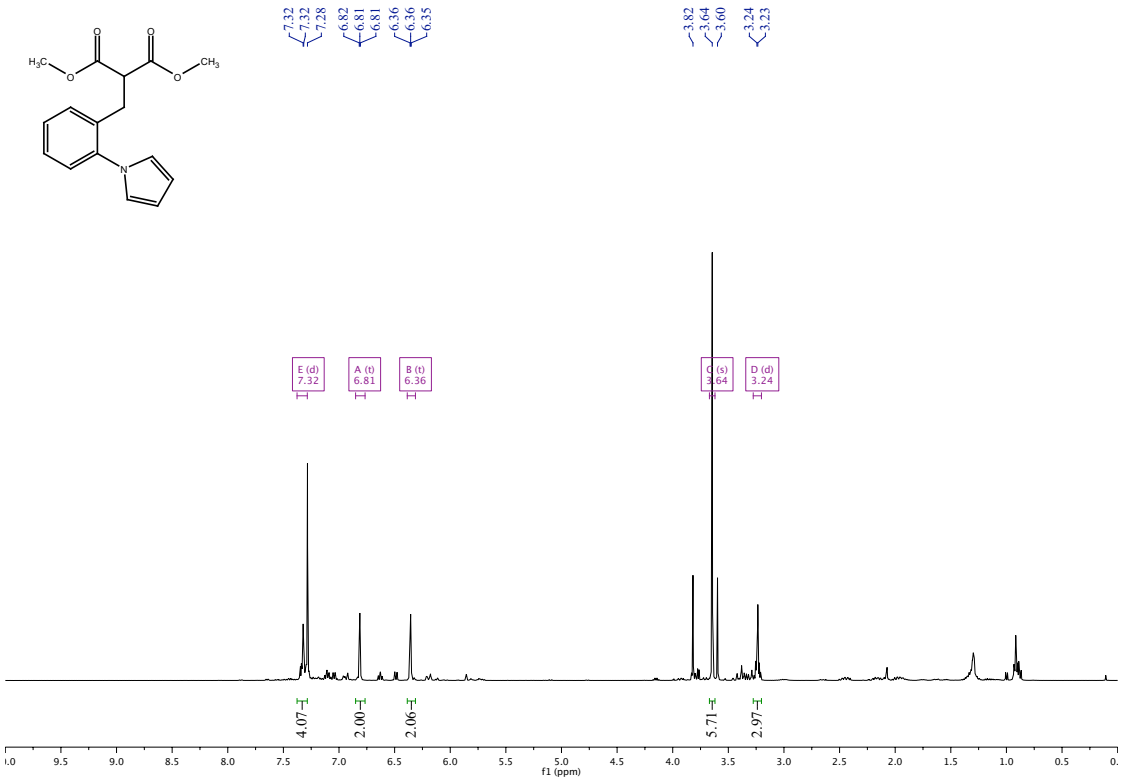
4.2c


O
N
CH2
H2C
A (d) 10.38
C (ddd) 7.52
H (m) 7.11
B (dd) 7.80
G (m) 7.17
D (m) 5.89
F (dddd) 5.24
E (dt) 3.83
1.00
1.03
1.11
1.07
1.12
2.25
4.82
4.70
f1 (ppm)

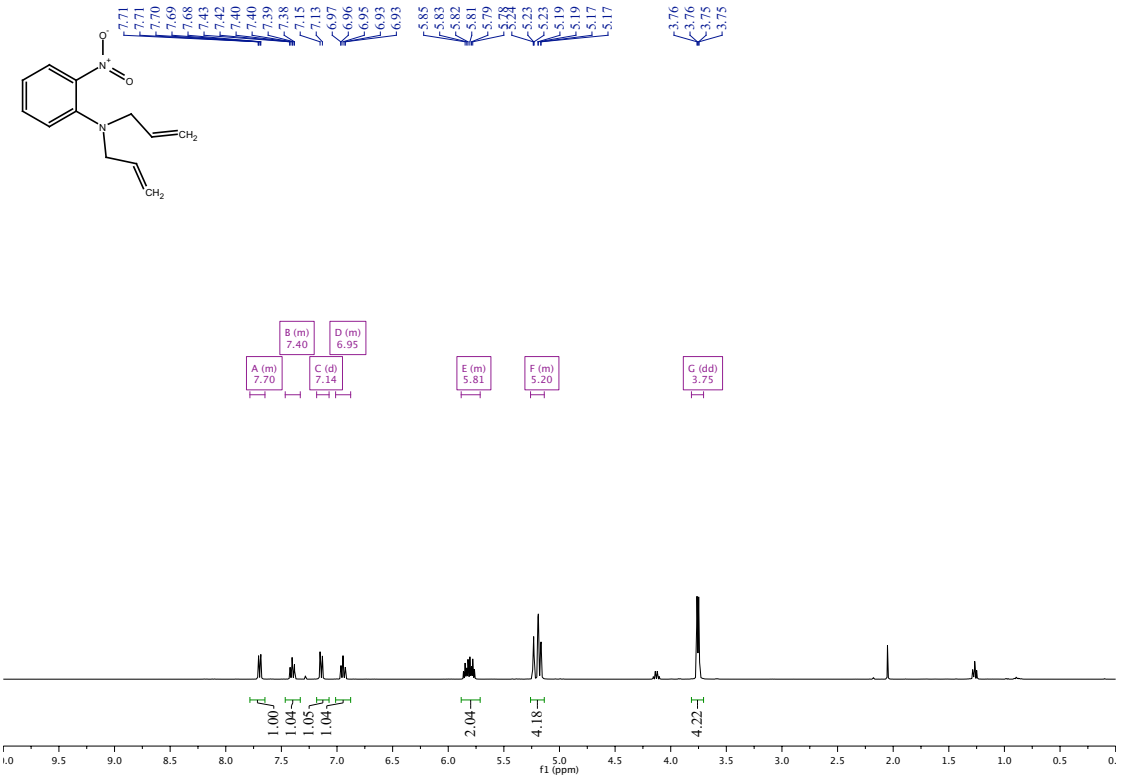
4.1b


10.14
7.74
7.74
7.73
7.72
7.44
7.44
7.43
7.42
7.42
7.41
7.40
7.28
6.85
6.83
6.81
6.79
5.94
4.22
A (s) 10.14
B (dd) 7.73
C (ddd) 7.42
D (dd) 6.82
E (s) 5.94
F (s) 4.22
1.00
1.00
1.10
2.26
2.17
4.24
f1 (ppm)

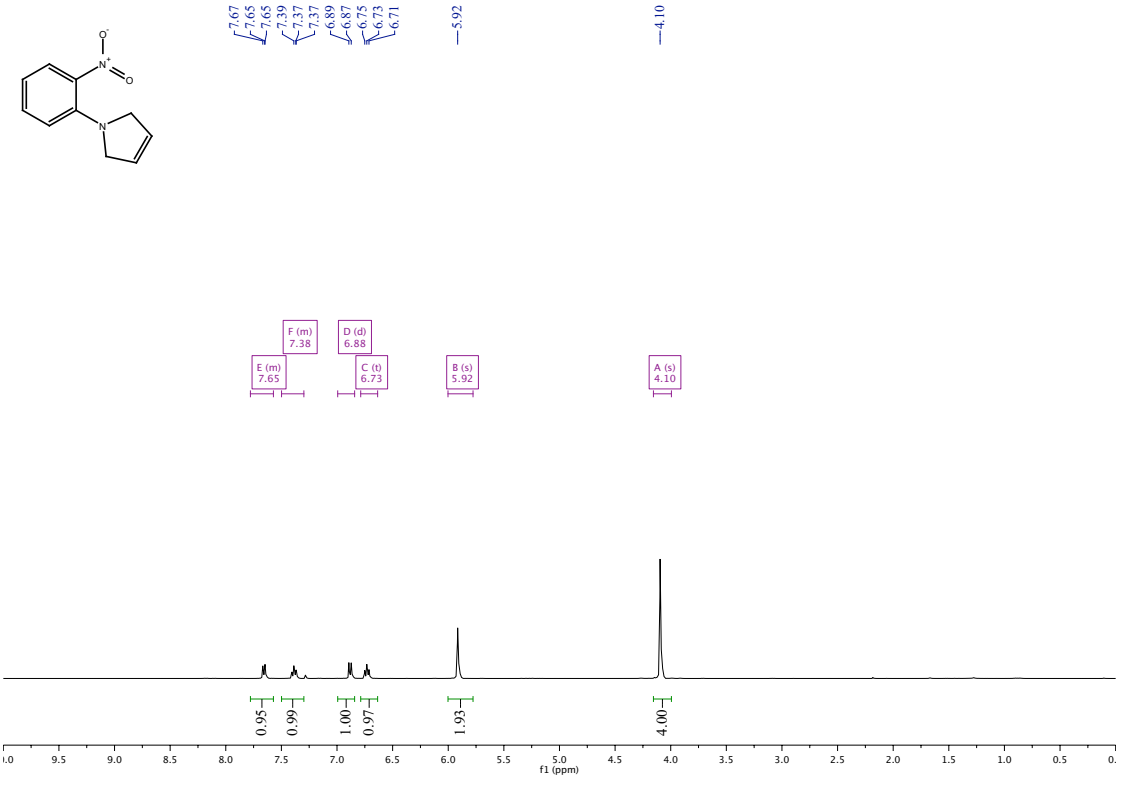
4.4a


7.32
7.32
7.28
6.82
6.81
6.81
6.36
6.36
6.35
3.82
3.64
3.60
3.24
3.23
E (d) 7.32
A (t) 6.81
B (t) 6.36
C (s) 3.64
D (d) 3.24
4.07
2.00
2.06
5.71
2.97
f1 (ppm)

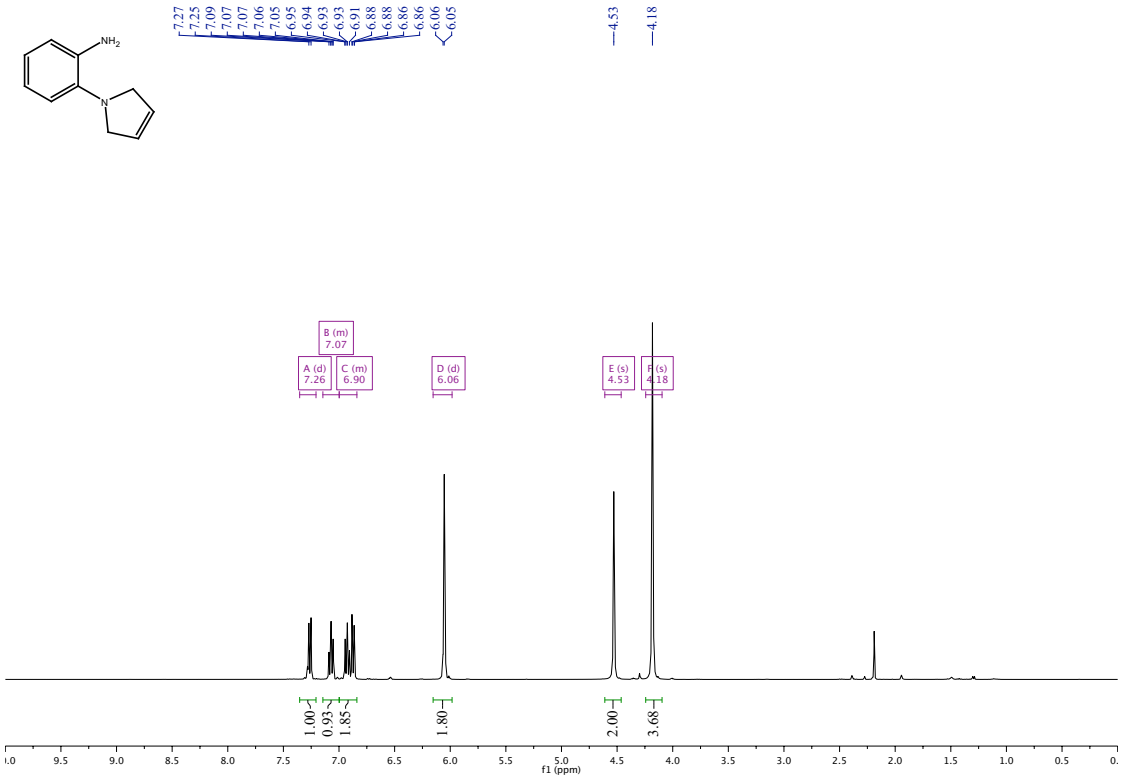
4.5b


7.71
7.71
7.70
7.69
7.68
7.43
7.42
7.40
7.40
7.39
7.38
7.15
7.13
6.97
6.96
6.95
6.93
6.93
5.85
5.83
5.82
5.81
5.79
5.23
5.23
5.19
5.19
5.17
5.17
3.76
3.76
3.75
3.75
B (m) 7.40
D (m) 6.95
A (m) 7.70
C (d) 7.14
E (m) 5.81
F (m) 5.20
G (dd) 3.75
1.00
1.04
1.05
1.04
2.04
4.18
4.22
f1 (ppm)

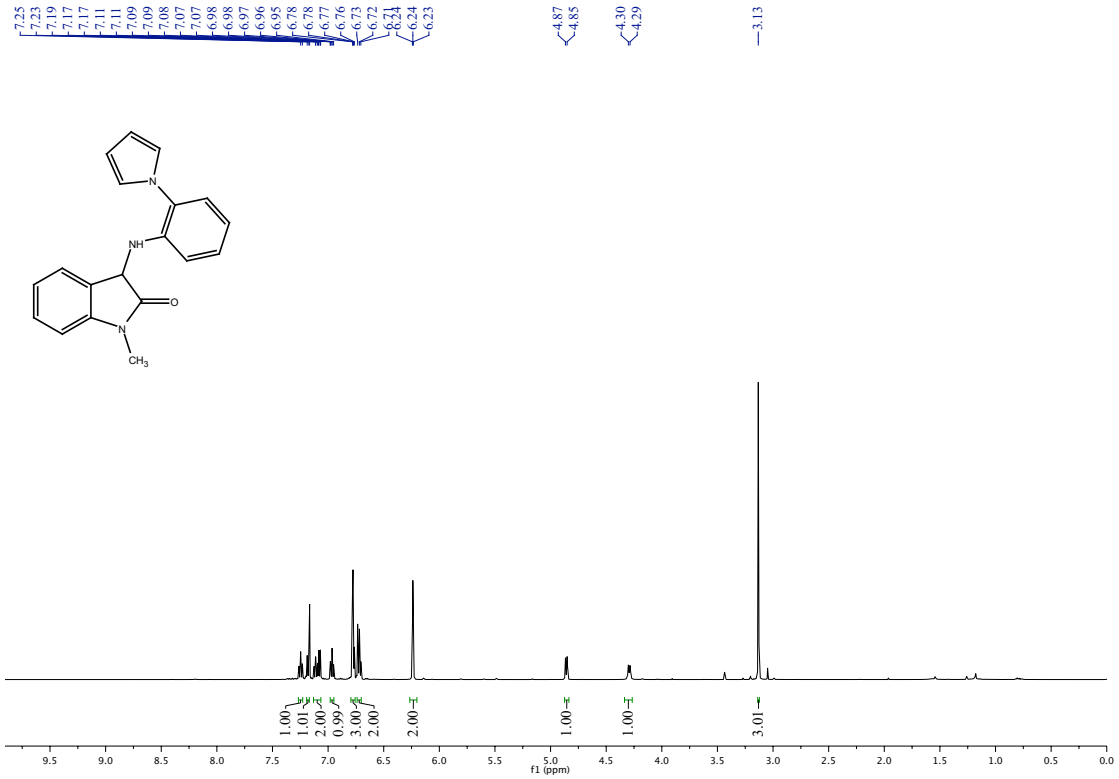
4.5c


7.67
7.65
7.65
7.39
7.37
7.37
6.89
6.87
6.75
6.73
6.71
5.92
4.10
F (m) 7.38
D (d) 6.88
E (m) 7.65
C (t) 6.73
B (s) 5.92
A (s) 4.10
0.95
0.99
1.00
0.97
1.93
4.00
f1 (ppm)

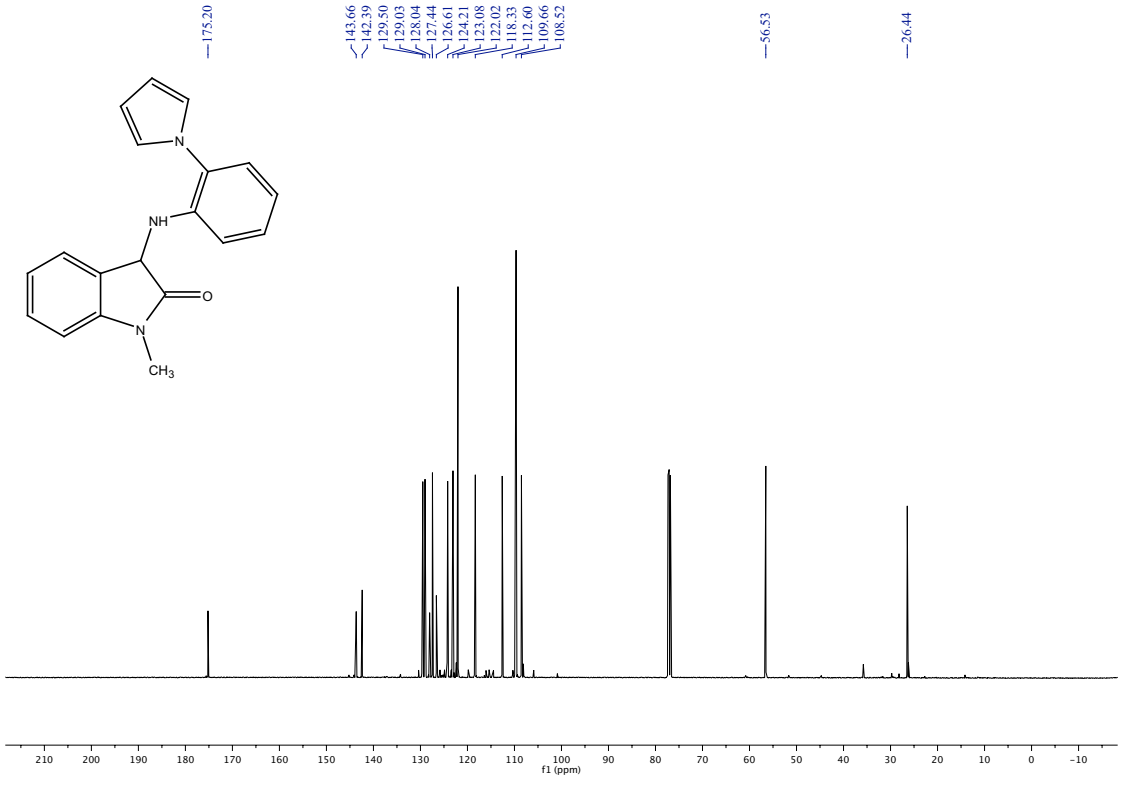
4.5d


7.27
7.25
7.09
7.07
7.07
7.06
7.05
6.95
6.94
6.93
6.93
6.91
6.88
6.88
6.86
6.86
6.06
6.05
4.53
4.18
B (m)
7.07
A (d)
7.26
C (m)
6.90
D (d)
6.06
E (s)
4.53
F (s)
4.18
1.00
0.93
1.85
1.80
2.00
3.68
f1 (ppm)

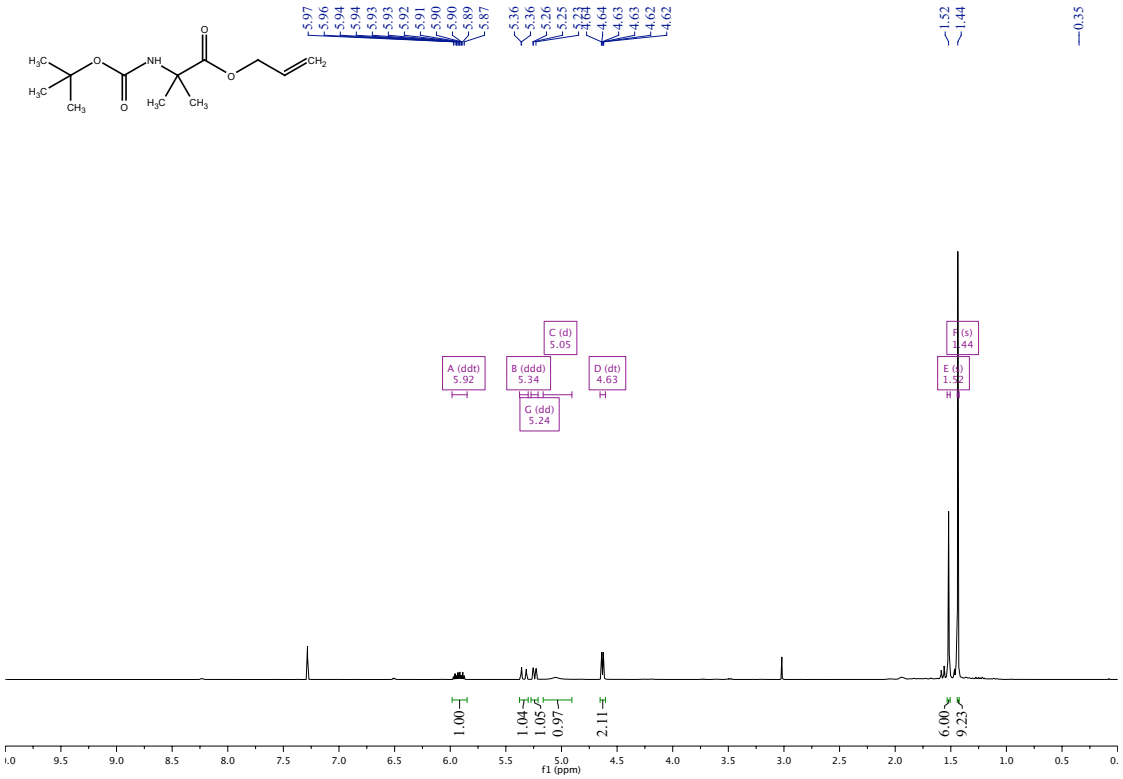
4.5a



4.5a Carbon

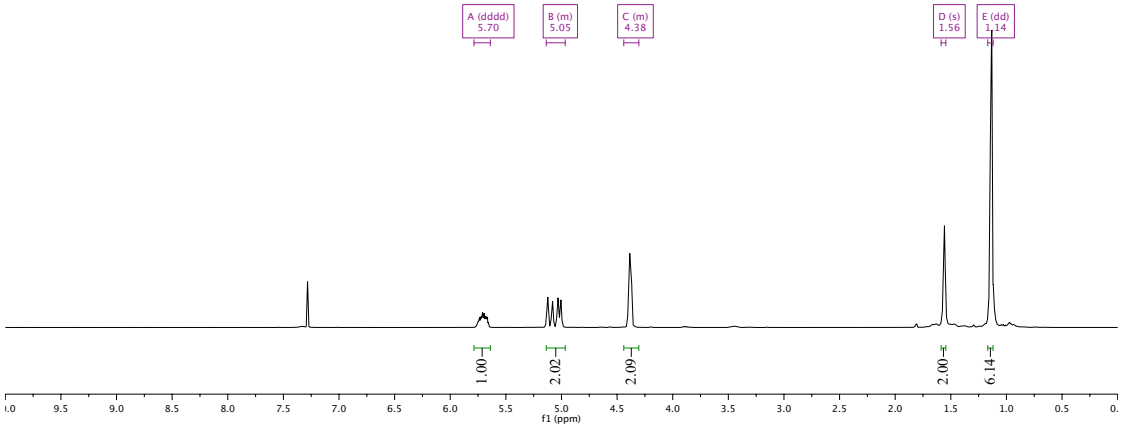


4.6c

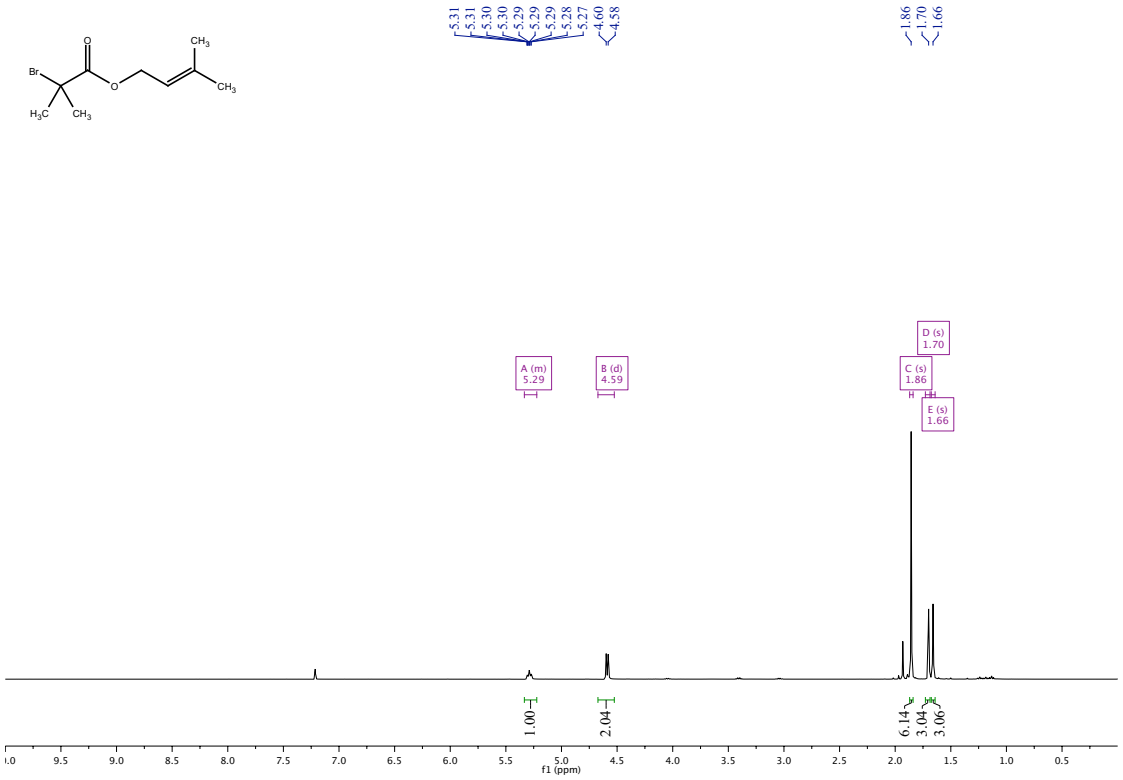


4.6d

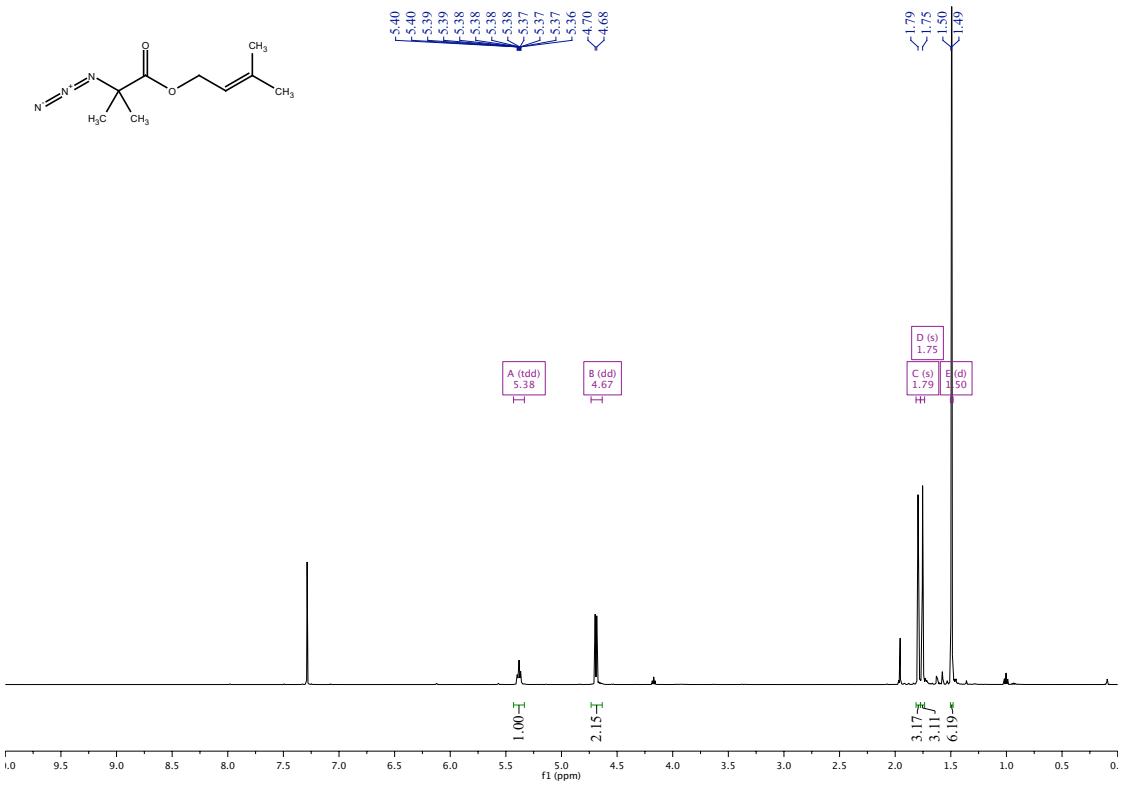
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (dddd, J = 10.5, 5.6, 2.7, 1.4 Hz, 1H), 5.12 – 5.03 (m, 2H), 4.44 – 4.30 (m, 2H), 1.56 (s, 2H), 1.14 (dd, J = 5.3, 3.4 Hz, 6H).



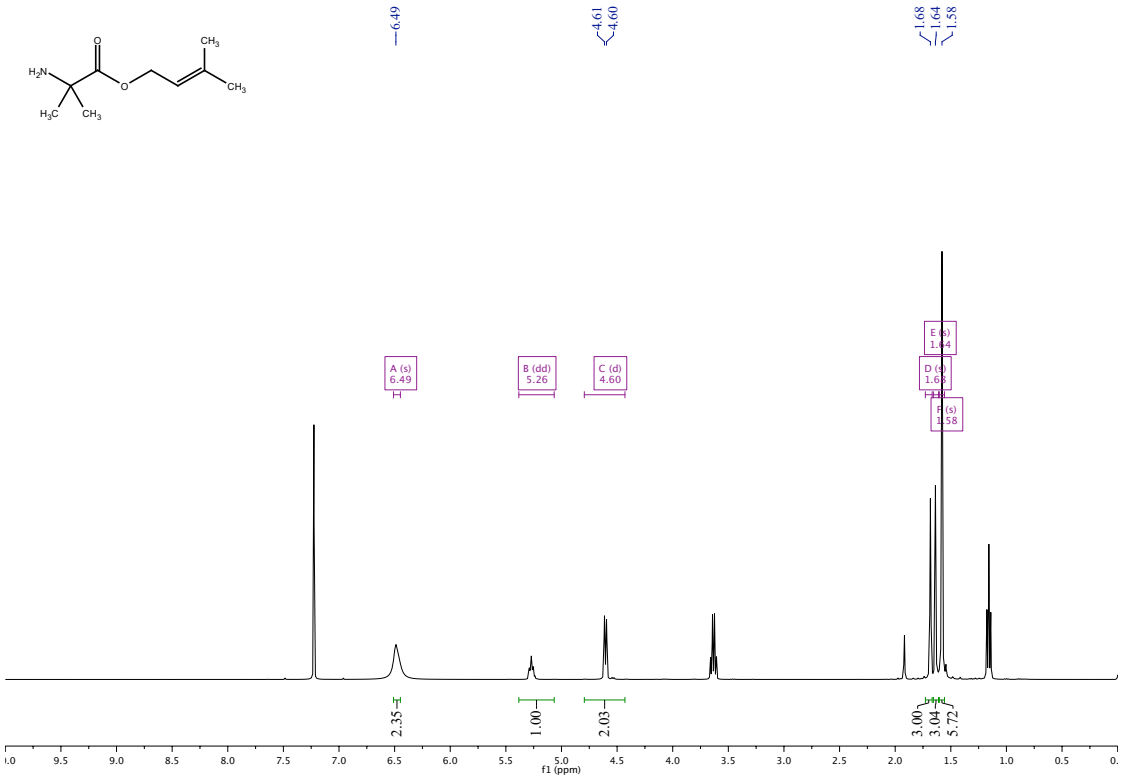
4.7a

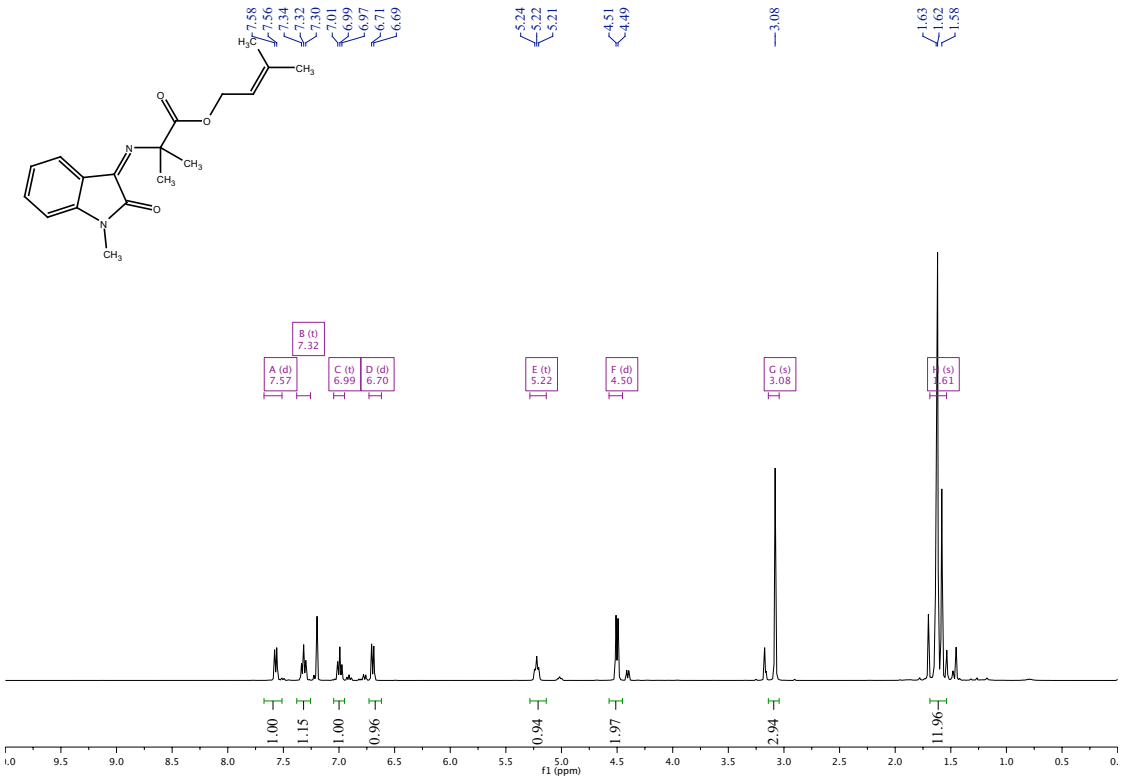

5.31
5.31
5.30
5.30
5.29
5.29
5.29
5.28
5.27
4.60
4.58
1.86
1.70
1.66
A (m)
5.29
B (d)
4.59
D (s)
1.70
C (s)
1.86
E (s)
1.66
1.00
2.04
6.14
3.04
3.06
f1 (ppm)

4.7b

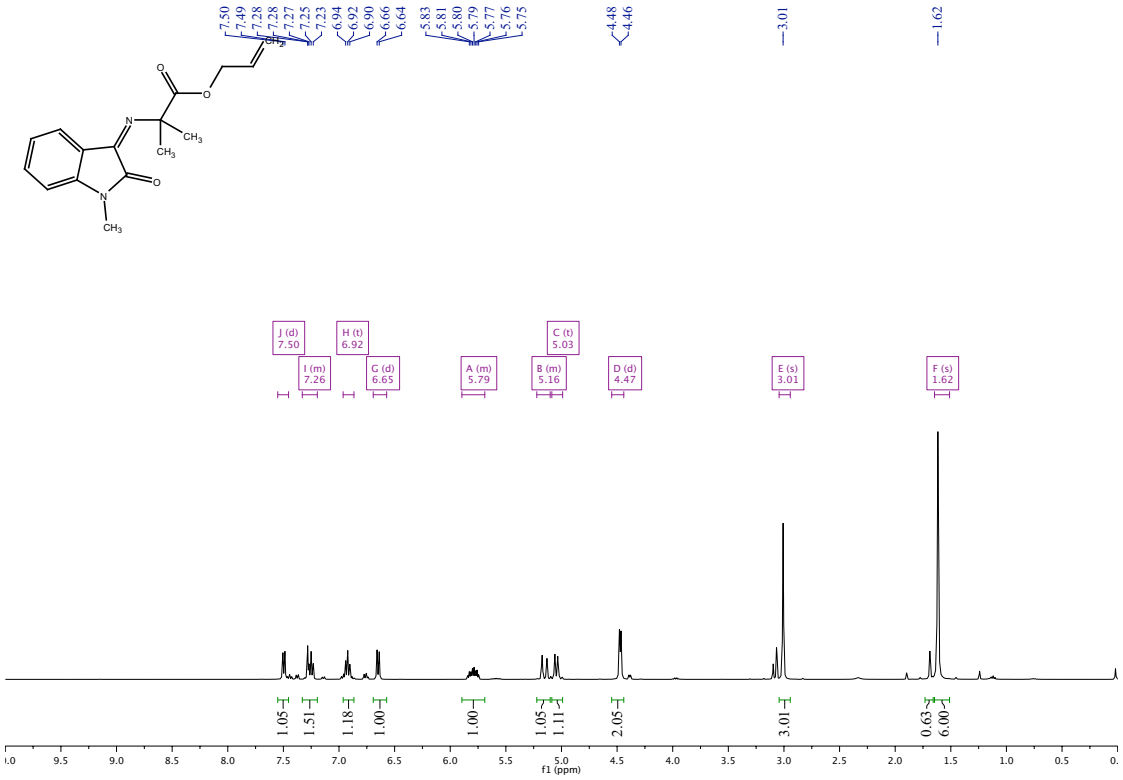

5.40
5.40
5.39
5.39
5.38
5.38
5.38
5.38
5.37
5.37
5.37
5.36
4.70
4.68
1.79
1.75
1.50
1.49
A (tdd)
5.38
B (dd)
4.67
D (s)
1.75
C (s)
1.79
E (d)
1.50
1.00
2.15
3.17
3.11
6.19
f1 (ppm)

4.7c

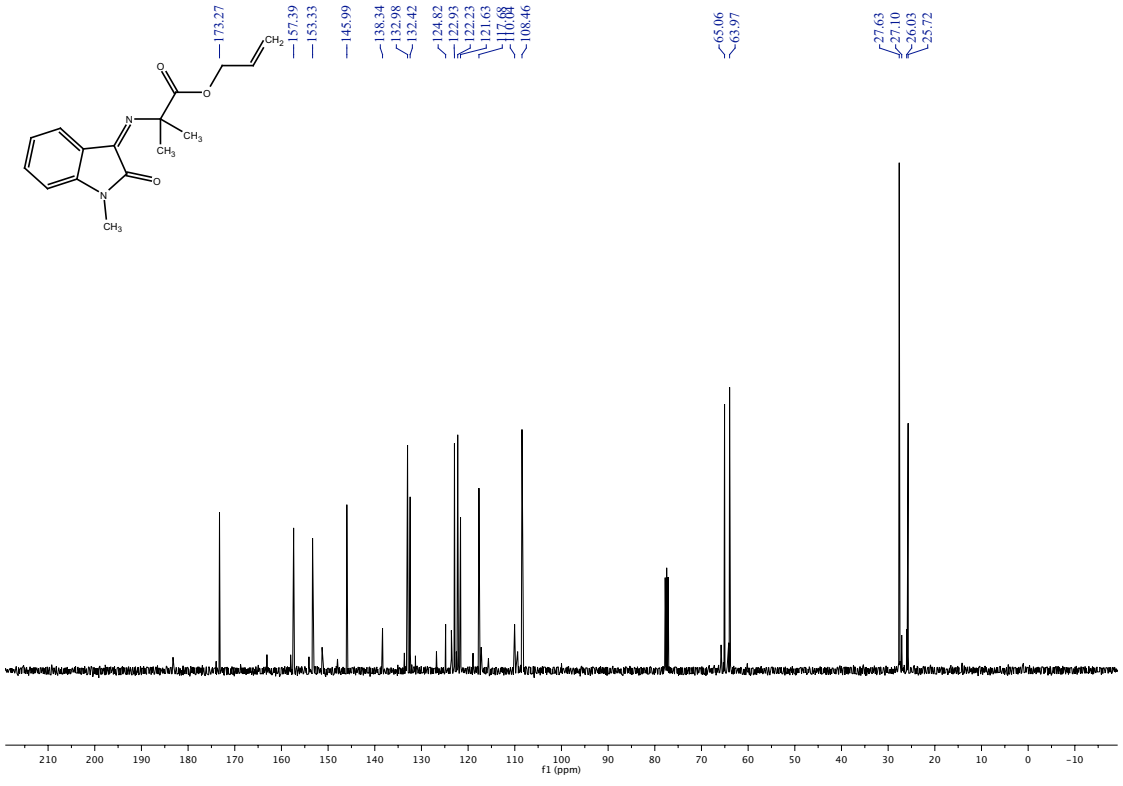

6.49
4.61
4.60
1.68
1.64
1.58
A (s) 6.49
B (dd) 5.26
C (d) 4.60
E (s) 1.64
D (s) 1.63
F (s) 1.58
2.35
1.00
2.03
3.00
3.04
5.72
f1 (ppm)


7.58
7.56
7.34
7.32
7.30
7.01
6.99
6.97
6.71
6.69
5.24
5.22
5.21
4.51
4.49
3.08
1.63
1.62
1.58
B (t) 7.32
A (d) 7.57
C (t) 6.99
D (d) 6.70
E (t) 5.22
F (d) 4.50
G (s) 3.08
H (s) 1.61
1.00
1.15
1.00
0.96
0.94
1.97
2.94
11.96
f1 (ppm)

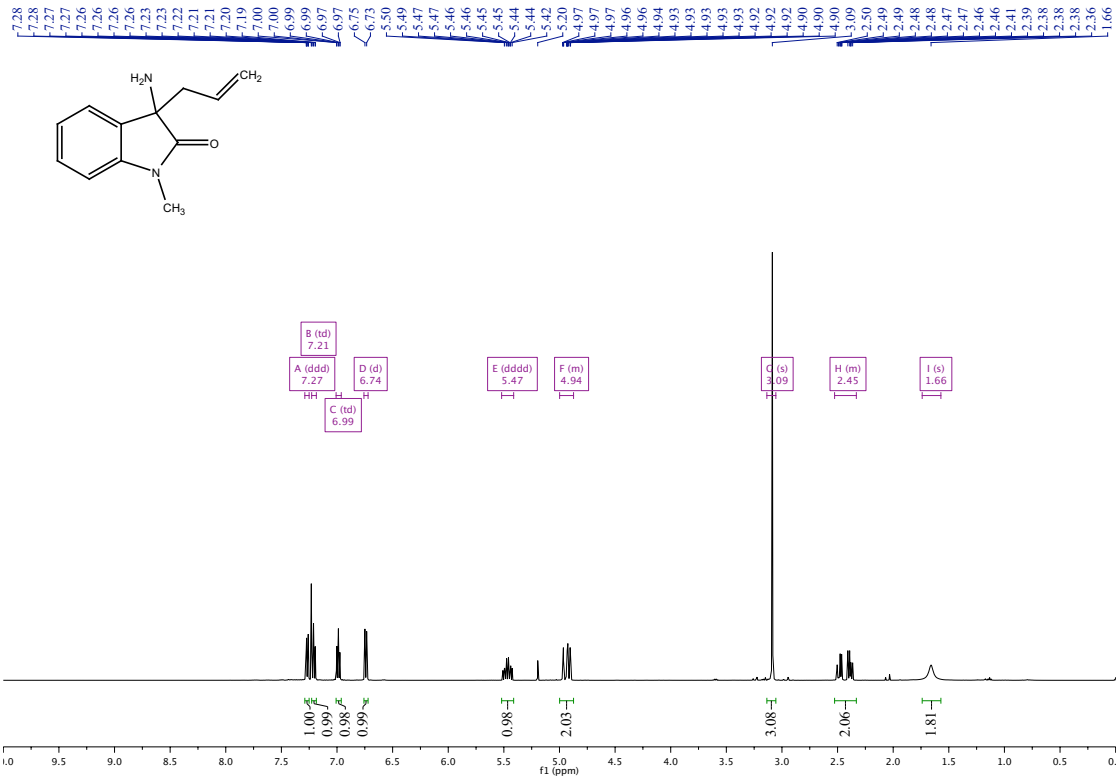
4.6e



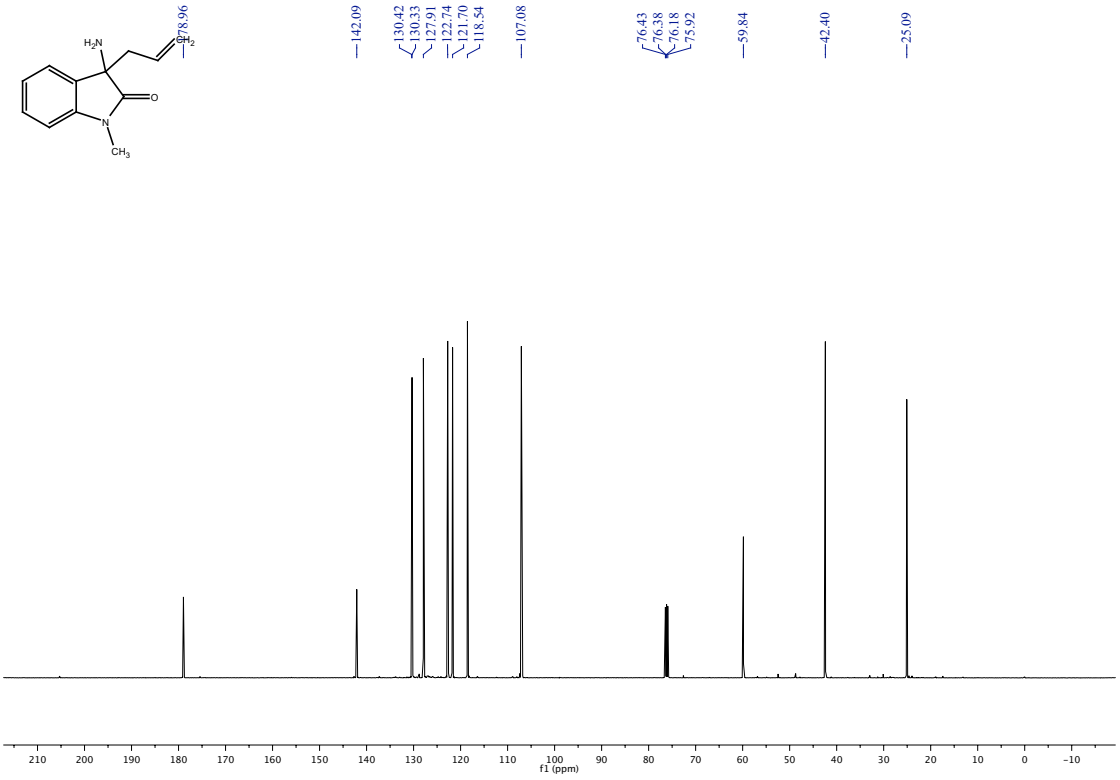
4.6e Carbon



4.6a



4.6a Carbon


H2N
O
N
CH3
CH2
118.96
142.09
130.42
130.33
127.91
122.74
121.70
118.54
107.08
76.43
76.38
76.18
75.92
59.84
42.40
25.09
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)